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A.M.A. JOURNAL OF

DISEASES OF CHILDREN

American Pediatric Society

Sixty-Eighth Annual Meeting
Atlantic City, N. J.
May 8 and 9, 1958

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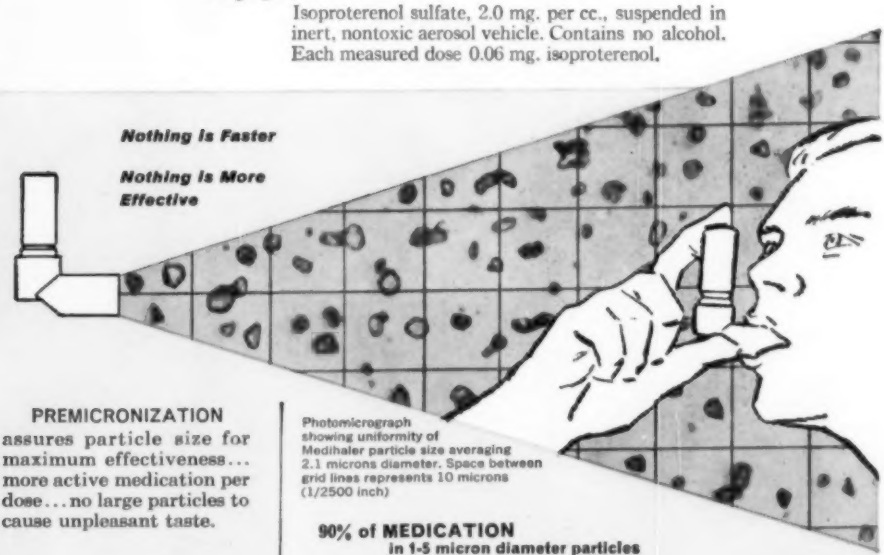

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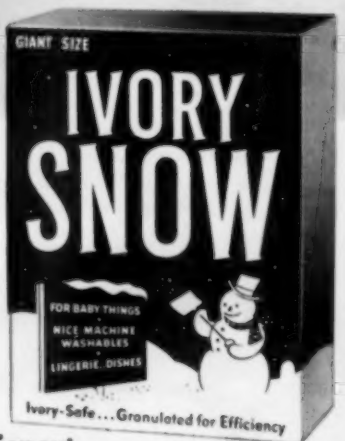

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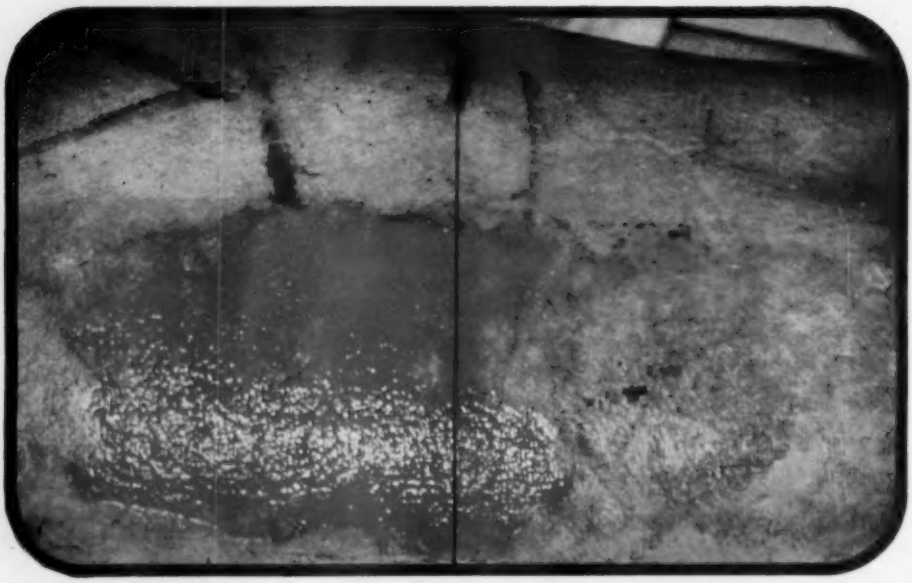

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Milestones in Scientific Pediatrics

A. ASHLEY WEECH, M.D., Cincinnati

From time to time throughout the torrid summer in Cincinnati, I am compelled to yield to forces of nature as ineluctable as time and tide and—mow the lawn. The instrument used for this purpose has no built-in source of power. To make it work, I have to give generously of myself. I am always amazed at the pervading sense of satisfaction once the chore is done. With censurable vanity I am prone to fetch a cold can of beer and, while slowly sipping, survey the new beauty of the nicely trimmed grass. Indeed, I glory in the sight of *le fait accompli.*

One of the most rewarding aspects of being president of the American Pediatric Society is the awareness that it brings of the affection of many friends. Since you have made me feel that the affection is real, perhaps you will indulge me a bit further and listen with tolerance to the content of a presidential address prepared for those members of the Society who are able to derive satisfaction and more than a little happiness from surveying what has been done in the past. For a while when I started my cogitations, the still small voice of conscience insistently reminded me that I should use this occasion to predict the future and, of course, unknown destiny of pediatrics. But, I was frightened by the lack of the requisite wisdom. Then, with further contemplation I abandoned the thought entirely, reflecting that "even if I had the gift of prophecy and understood all mysteries and all knowledge," no one would believe me anyway. Again I was astounded by the power of the Anglo-Saxon mind to rationalize its problems in favor of expediency.

Having reached the major decision to dodge the role of the prophet and review selected events over the period of my personal medical life, there remained the need to decide which events were to be reviewed. We have had fun in making a selection. I use the first person plural because an immediate step was to call a meeting of the full-time staff of the Cincinnati Pediatrics Department and ask for suggestions. The address today is therefore possibly unique in the annals of presidential dissertations in that the thoughts to be covered were contributed and discussed by a considerable number of colleagues. God bless them! In the course of the departmental discussion, there was quick agreement that the truly great advances in the medical renaissance of the last few generations have been less concerned with the solution of specific problems than with the development of new methods of logical thinking, or new methodology, which are applicable in expanding collateral fields. I shall cite examples of these happenings as the essay unfolds.

First, I should like to discuss a few pertinent aspects of the story of the conquest of rickets. The story involves many people and much persistent research. I

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Presidential Address, American Pediatric Society, Atlantic City, N. J., May 8, 1958.

can name here only a few of the people, for a main purpose will be to show how an unanticipated outcome of one event in the story has been of profound importance to medical progress in almost countless different fields. The American Pediatric Society can justly be proud of contributions by many members toward the eradication of rickets. John Howland; Ned Park; Paul Shipley; Ben Kramer; Grover Powers; Alfred Hess; Philip Jeans; Sam Karelitz; Ethel Dunham; Martha Eliot; Emmett Holt Jr., and others come quickly to mind as protagonists in the exciting theater of scientific drama rushing toward a triumphal climax. There is luster in what each of them did. But I am immediately concerned with the status of knowledge in the mid-twenties and of events that soon ensued.

By the spring of 1925 it had been established that: (*a*) the antirachitic dietary factor was distinct and different from the fat-soluble vitamin A; (*b*) both human and experimental rickets could be prevented or cured either by cod-liver oil or by exposure to ultraviolet light; (*c*) many common foodstuffs developed antirachitic potency after exposure to ultraviolet rays; (*d*) the active ingredient of cod-liver oil was present in the nonsaponifiable fraction of the oil; (*e*) cholesterol or a closely related sterol could be rendered antirachitic by ultraviolet irradiation, and (*f*) activation of cholesterol was attended by a change in its optical spectrum.

Alfred Fabian Hess of New York was at the time very much aware of all of these items of recent knowledge. Indeed, most if not all of the items had been confirmed in his laboratory. Hess also knew that there lived in Göttingen, Germany, a chemist by the name of Adolf Windaus, who had devoted his life to studying and classifying compounds related to cholesterol. Accordingly, in March, 1925, Hess wrote to Windaus in an attempt to persuade this sterol master to join in the fight against rickets. The attempt was at first not successful. Windaus replied courteously, but he did not accede to Hess' request for active collaboration. More than a year later in May, 1926, Hess again approached Windaus, summarizing recent findings and asking for a series of cholesterol derivatives which he (Hess) would test for antirachitic potency after exposure to ultraviolet light. This time the appeal bore fruit. There followed an exchange of many letters and active experimentation on both sides of the Atlantic. A suggestion originally made by Rosenheim and Webster that the steroid substance capable of being activated by the mercury vapor lamp was not cholesterol itself but rather a contaminant became increasingly plausible and later practically certain when it was shown that purified cholesterol recovered after bromination could no longer be activated by irradiation. Windaus sent to Hess quite a number of cholesterol derivatives. The first reports of this cooperative enterprise published in November, 1926, and January, 1927, were concerned with negative results.[1,2] Then, in the February, 1927, issue of the *Proceedings of the Society for Experimental Biology and Medicine* there appeared a paper by Hess and Windaus entitled "The Development of Marked Activity in Ergosterol Following Ultraviolet Irradiations."[3] Rickets had been cured in rats by as little as 0.003 mg. per capita daily. The paper is a beautiful example of commendable brevity. It is composed of 206 words, less than half the number of words allowed for the abstracts of papers to be presented at this meeting. It ends with the terse comment: "This is a complete report." The next year, 1928, Windaus was awarded the Nobel Prize in chemistry for work that culminated in this report.

It is not my purpose this morning to bemoan the fact that Hess himself was not similarly honored. Murray Bass has touched on this point in his splendid Pediatric Profile of Alfred Hess.[4] It has turned out, however, to have been of extreme importance that Windaus received acclaim.

The experience of Hess in 1925 of being unable to persuade an organic chemist to collaborate actively in solving a medical problem was by no means unique. By and large, research in the basic sciences, in its effort to achieve the status of applied research, was oriented toward industry and not toward biology and medicine. All of this changed when Windaus was awarded the Nobel Prize. Indeed, in 1929 Hess himself complained that the number of communications appearing from laboratories of pure as well as of applied science had become so great as to make it almost impossible to keep pace with them.[5] The efflorescence of contributions from these new sources goes on in ever-increasing abundance. Humanity has been reaping a harvest in terms that a child can comprehend.

No survey of what has transpired in medicine during my life as a doctor would be complete without some mention of the many triumphs in the war on infectious disease. Immunizing procedures, therapeutic sera, and antibacterial agents have forced a steady retreat of the armies of hostile micro-organisms. Some diseases are vanquished and will, I think, never again wage a victorious counterattack. With effective methods of treatment, other diseases have been robbed of their horror. In this latter category I am at once thrilled and amazed by spirit-stirring successes in battling all sorts of purulent meningitis, including that due to tuberculosis, and also by prophylactic results in the campaign against rheumatic heart disease. In the former group is diphtheria, a disease which has practically vanished. Although I would not wish its return, I may perhaps be pardoned for recalling nostalgically the thrill of popping an O'Dwyer intubation tube through the glottis of a strangling child and watching his expression of wonder that he again could breathe. Congenital syphilis is today almost unknown, and I have no nostalgic regrets. With the decline in syphilis we have learned of other infections that can strike at the unborn child—rubella, toxoplasmosis, homologous serum hepatitis, herpes simplex, and cytomegalic inclusion disease. A moment ago I expressed pride in what had been done to combat purulent meningitis. Nevertheless, fulminating meningococcus septicemia with or without meningitis remains as a terrifying and all too common specter. All of these conditions present a challenge for triumphs of the future. In addition, the Nobel Prize-winning roller-tube culture discovery of Enders, Robbins, and Weller is being used to disclose a new list of infections to replace those that are gone. We shall hear about some of these later in the morning. In the meantime, I wish to pay tribute to members of this Society who have waged a rewarding struggle against the infections of the past. Jim Trask, Harold Faber, Hattie Alexander, Albert Sabin, Margaret Smith, May Wilson, John Toomey, Bill Bradford, Horace Hodes, and Ann Kuttner stand out in recollection. I am vainglorious about what they have done.

In view of the circumstances, it is interesting that a staff colleague should state during our group discussion that pediatricians, being busy with other affairs, have not done important work in discovering new antibiotics. In a purely literal way the statement is correct. But, it is justifiable to cite in rebuttal that pediatricians were among the first to recognize the significance of events unfolding in this area. In 1941 the E. Mead Johnson Award of the American Academy of Pediatrics was given to René Dubos [6] of the Rockefeller Foundation. This was a remarkable choice since Dubos was neither a pediatrician nor even a doctor of medicine. Because of the clairvoyant vision of what the future had to bring, it seems worth while to record the names of the members of the Awards Committee. They were Irvine McQuarrie (Chairman), Charles Anderson Aldrich, Harold Kniest Faber, Oscar Menderson Schloss, and Edwards Albert Park. The highly esteemed members of this committee might equally well have been representing the American Pediatric Society.

What had Dubos done to merit citation by a pediatric Awards Committee? For a period of 9 or 10 years he had been engaged in studying naturally-occurring enzymes capable of destroying organic compounds synthesized in living cells. By sheer inductive reasoning he had convinced himself that these enzymes simply had to occur in nature. "For every organic molecule synthesized during processes of growth," he argued, "there must be an enzyme to destroy it. For, if it were not so, that molecule would after eons possess the earth." Logic was supported by experimental demonstration that a substance could be extracted from soil capable of killing a long list of susceptible bacteria. The substance, which he named "gramicidin," developed in the soil after protracted exposure to several of these same bacteria. The work was done and the selection was made before the first announcement in England by Florey and associates [7] of clinical trials with penicillin. It has been said of Dubos that his demonstration and his reasoning made penicillin inevitable. What I wish to stress today is the far-reaching value of clear, simple, and convincing logic. As pediatricians we can be proud to have had representatives who were among the very first to recognize the worth of the thinking and of the investigations of a pioneer in a program destined to alter profoundly almost every field of medical practice.

Let us now turn the page for a quick glance at another astonishing development. Once again it is not the original discovery, important though it was, that commands attention but rather the effect of the finding on thinking in collateral fields. The investigation I am speaking of was described in a publication of November, 1949.[8] In it, Linus Pauling and colleagues reported identification by electrophoretic techniques of sickle hemoglobin and explained the nature of sickle-cell trait and sickle-cell disease on the basis of a single dose, as compared with a double dose, of an abnormal gene.

The fact that Pauling was not a pediatrician can scarcely detract from his genius. Nevertheless, it is of some interest to us today to note that Janet Watson, now associate professor of pediatrics at the State University of New York in Brooklyn, was also active in this field. In 1948 she had explained the failure of sickle-cell disease to occur in very young infants as resulting from the relatively large amounts of fetal hemoglobin in these infants.[9] The explanation was a real milestone of progress, and it led Dr. Watson to suspect that newly developed techniques and especially those of electrophoresis might reveal distinctive patterns in sickle-cell trait and sickle-cell disease. Only the lack of apparatus delayed her undertaking experiments in this connection until a short time before the announcement of Pauling et al. We pause for a moment of salute and then return to Pauling.

The California investigators understood fully the immediate implications of their findings. In substantiation I should like to quote from their classic paper.[8] "If the mechanism proposed . . . is correct, we can identify the gene responsible for the sickling process with one of an alternative pair of alleles capable through some series of reactions of introducing the modification into the hemoglobin molecule that distinguishes sickle-cell anemia hemoglobin from the normal protein." The sentence stresses that what is controlled by the genes directly is not the abnormal hemoglobin but rather a series of reactions leading to its formation. This important line of thinking is strengthened by a new methodology providing a clear and convincing method of distinguishing between a heterozygous and dominantly-transmitted trait and a homozygous and recessively-transmitted disease. The result of this announcement on ensuing thought and investigation by many scientists has been gratifying and far-reaching. Not only has there been identification of at least 11 abnormal hemoglobins, but also enthusiasm has been engendered for further re-

search in the entire group of disorders that are catalogued as inborn errors of metabolism. It is of more than passing interest that the basic nature of these diseases was first guessed by Sir Archibald Garrod[10] as long ago as 1908. In the attempt to support his concepts with experimental evidence, Garrod was indefatigable in using every then available technique in his search for elusive facts. He was ahead of his times. We hail him for the greatness of his dreams even though genuine progress had to await the birth of a new methodology. To the technique of electrophoresis there has been added paper chromatography. Chromatograms have made it possible to scan body fluids rapidly for hundreds of metabolites. The reward indeed is great. Understanding of the enzyme-controlled chemistry of normal physiologic processes and of the genesis of hereditary diseases is literally leaping ahead.

In view of these developments it is likely that many and perhaps all genetically determined congenital malformations are the result of defects in the enzymes controlling organogenesis in the embryo. Although I promised not to predict the future, it is exciting to think that methods will someday be found to identify the nature of these chemical processes, that with the knowledge may come the means of preventing the deformities.

Comprehension of the causes of congenital malformations has also traveled a long way from the tacit assumption that all or nearly all of these defects are fashioned by the genes. Phenocopies have been defined as "the spittin' image" of genetically determined monstrosities, and their cause is now known to reside in factors of environment. In a relatively few years we have learned that teratologic agents may be nutritional, infectious, actinic, chemical, or hormonal. In giving credit, the American Pediatric Society will, I know, be indulgent if I bow in respect to my friend and Cincinnati colleague, Josef Warkany. Before leaving the subject it is important to take note that some of the anomalies of environmental causation are iatrogenic in origin. The most recent member of this group is female pseudohermaphroditism resulting from testosterone-like drugs administered early in pregnancy to ward off threatened abortion.[11,12] In all such situations the physician carries a unique burden of responsibility.

The last few decades have brought not only enhanced understanding of congenital malformations but with it also great forward strides in techniques of corrective surgery. And, in turn, the possibility of helpful surgery has stimulated the development of new and powerful diagnostic techniques. In no area has the pace of progress been more impressive than in the newer management of congenital heart disease. My hat is off to Helen Taussig, a member of this Society, not only for visualizing the benefits of an artificial ductus for patients with Fallot's tetrad but also for demonstrating that an accurate diagnosis is often possible on clinical grounds alone! But, there followed at bewildering speed a series of further steps toward precision diagnosis. Development of methods of measurement during right heart catheterization meant a Nobel Prize for Richards, Cournand, and Forssmann. Angiocardiography was born and from the technique stemmed diagnostic angiograms in many collateral fields. Better x-ray tubes and faster x-ray film were accompanied by the need for mechanically elaborate casette-changing devices so that several pictures could be taken per second as radiopaque material moved through the chambers of the heart. These devices are in turn being superseded by what can be done with an electronic image intensifier. It is now possible to photograph a moving x-ray image on a fluoroscopic screen at a rate of 60 frames per second. We shall hear more about this technique in a paper to be presented by Dr. Silverman tomorrow afternoon. These inventions are showing a welcome usefulness in keeping diagnosis abreast of startling advances in cardiac sur-

gery and particularly those surgical procedures that depend on direct visualization of the chambers of the heart during perfusion with a pump oxygenator.

It is now my duty to bring an essay to a close. There has been no time even for mention of other items of progress suggested by my colleagues. In the mood of dreams I see a swift parade of discoveries and beside the discoveries I see distinguished men—new hormones, an alphabet of vitamins, artificial kidney, tracer isotopes, Rh factor, photoelectric cell, thermionic amplifier, cathode-ray oscillograph, electric spectrophotometer, Warburg apparatus, flame photometer, and so on. All of these have served their masters in unraveling the entangled threads of physiology and all have played a part in the relief of human suffering. I can only wonder if the youngest members of this Society will three decades hence be able to look back on a more exciting period in the development of methodology or on more illustrious men who made and applied the methods in the conquest of disease.

The Children's Hospital (29).

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Presentation of the John Howland Metal and Award of the American Pediatric Society to Dr. Irvine McQuarrie

At the Sixty-Eighth Annual Meeting, May 8, 1958, Atlantic City, N. J.

INTRODUCTION AND PRESENTATION BY DR. ARILD E. HANSEN

Mr. President, Dr. McQuarrie, Fellow Members and Guests of the American Pediatric Society:

Activators are either congenitally endowed or their particular properties must be acquired, but no matter how great the potential, the conditions must be created for them to exercise their power. In attempting to delineate the congenital from the acquired factors concerning the man who today is being honored, the answer is not clear even after careful investigation. That he is an "activator" must be admitted and the evidence is abundant.

Irvine McQuarrie was born in Silver Reef, Utah, in the early nineties, his grandparents having ventured into the alluring western country about a century ago. His father owned and ran a thriving gold mine. Early in the twentieth century, Irvine spent many a summer next to nature tracing streaks of gold ore. As seemed quite logical in the light of his environment and experience, he pursued the field of mining engineering and in 1915 he was awarded the B.A. degree from the University of Utah. During the interim he had the good fortune to meet an attractive, capable, and gracious "guide" of unlimited potential energy, Miss Vira Perkins, who similarly was reared in an environment where adventure and pioneering were tantamount to life itself. To Vira, whom nature endowed with charm and perpetual patience, must be credited understanding and the indispensable role of fostering the development of her husband's career. Three delightful daughters made possible the fulfillment of an ideal family life during the unfolding of the distinctive personality which catalyzes reactions capable of bringing out the best in others.

For reasons known to himself, Dr. McQuarrie transferred his interest to the strictly biologic field, and in 1915 he went to the University of California Medical School and in 1917 joined the staff of the Hooper Foundation of the University of California as a research fellow. There is no doubt that his career was influenced profoundly by one of our great men in medicine, Dr. George H. Whipple. Irvine's sharp and discriminating memory made it possible for him to absorb the unlimited pounding of activating particles from the many powerful forces present in that stimulating group of western men. After receiving the degree of Doctor of Philosophy in 1919 and completing the first two years of medical school, he moved on to Johns Hopkins School of Medicine.

Trite, indeed, would it be to say that he received and stored energy units from the many powerful cerebral cyclotrons present in the illustrious faculty of that institution. It was as a student that he absorbed the penetrating rays of lasting stimulation put forth by the person whose name has become synonymous with distinction in pedi-

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atrics. In addition to the spiritual guidance received from Dr. John Howland, Irvine sought out and was sought out by those bearing his secondary radiations. Some of these men already have been named recipients of the Howland Award.

How many original ideas flashed through the youthful McQuarrie's mind will never be known; however, periodically many of these scintillations were captivated, balanced, and stabilized, as is manifest by his diverse publications during the past four decades. In rereading his communications there are evidences of originality, clearness of thought, and clarity of expression, which characterize his writings. From personal experience it may be said that he has been his own severest critic. While still a student we detect evidence of Dr. McQuarrie's Pandora-like curiosity. He conceived the idea that the mother could be the victim of noxious agents produced by her indwelling heir and in Volume 34 (1923) of the *Bulletin of the Johns Hopkins Hospital* we learned that toxemia of pregnancy occurred 16½ times more frequently when the maternal and fetal blood groups were incompatible than when they were in the same isoagglutination group. Shortly after, Ottenberg (J. A. M. A. 81:295, 1923) presented speculations to suggest that isoagglutination probably is not the cause of eclampsia, but he offered the idea that this phenomenon may be a factor in icterus gravis. Following the discovery of the Rh factor a number of years later, some workers, in pursuing the problem of erythroblastosis fetalis, were encouraged in their endeavors by the work of McQuarrie relative to isoagglutination between maternal and fetal blood.

In 1921 Dr. McQuarrie became a House Officer at the Henry Ford Hospital in the Department of Medicine and Pediatrics and in 1923 was made Director of the Section of Endocrinology and Metabolism. During this interval "pediatrics" was in the prepubescent spurt of development. Some astute 'selector of men' pursuaded him to go solidly into children's diseases and in 1924 we find him associated with Drs. Edwards A. Park and Grover F. Powers at Yale. He again returned to Detroit and was placed in charge of Pediatrics, but soon we find him enticed by his former "chief," Dr. Whipple, to return to the purely academic fold in Pediatrics at the University of Rochester.

At the 42nd Annual Meeting of the American Pediatric Society in 1930 we learned that Dr. McQuarrie expounded on the phenomenon of water retention from sustained antidiuresis following the administration of vasopressin (Pitressin). He reported that within 15 to 36 hours eight of nine children with mild epilepsy suffered a convulsive seizure; whereas, in a similar number of control subjects with equally great water retention, none experienced seizures. As is known to everyone here, Dr. McQuarrie arduously has probed into the question, "What triggers the convulsive episode?" and "What are the mechanisms concerned?" His studies expanded his horizons. Nature in her order of things probably compels one to reach new vistas simply by following the logical paths of basic truths.

Dr. McQaurrie believes that man is specially endowed with abilities to detect new things and is morally obligated to learn to understand life. To this end, he recognized that Nature herself supplies the clues but that the "experiments of Nature" must be studied so that man can advance. By following this philosophy, among other things, he observed, after the discovery of low serum sodium and high potassium in Addison's disease, that the opposite situation may occur in hypercorticoadrenalism. Along this line we may mention that: (*a*) tissue alterations may lead to metabolic errors in protein metabolism with inability to fabricate plasma proteins, perhaps a forerunner of the congenital agammaglobulinemia phenomenon; (*b*) the special endowment of the alpha cells of the pancreas to increase blood sugar; (*c*) the influence of fat as well as of carbohydrate in decreasing serum potas-

sium with precipitation of the paralytic state in patients with familial periodic paralysis; (*d*) the familial nature of spontaneously occurring hypoglycemia in infants, and (*e*) the spectacular cessation of hypoglycemic seizures with corticotropin (ACTH) and to a smaller degree with cortisone. Even if time were available, it would not be possible to relate in detail some of his many other and varied scientific accomplishments, to say nothing of his educational and social efforts towards man's better understanding of nature as well as of himself.

Among his social and economic activities, it may be mentioned that he initiated the Minnesota Memorial Society and played a leading role in establishing the University Investment-Retirement Association among the University of Minnesota Faculty with Investors Diversified Services, Inc. Never was he too busy to see anyone—all one had to do was "to wait him out." One day a fine older woman came to the University to talk to someone about "heart disease." After having been given a sort of "run around" by a number of other faculty persons, she landed in Dr. McQuarrie's office, she was listened to, and she, in turn, listened. Not too long after this visit and other happenings of similar nature, the Department of Pediatrics was the recipient of an endowment of over one and one-half million dollars.

I have a deep urge to return to my original thesis "Irvine, the Activator." During the time the young vigorous Irvine was hacking away at Nature's protective covering to seek the possible bonanza, the phenomenon of radioactivity was scarcely appreciated. Among the naturally occurring radioactive elements, i. e. congenitally endowed, we readily recognize K^{40}, Sn^{124}, Ra^{226}, Th^{232}, U^{235}, U^{238}, while among the activated elements, i. e. the acquired type, we have chosen to list B, B^{12}; Be, Be^{8}, Be^{9}; Ca, Ca^{45}; Co, Co^{60}; Cs, Cs^{134}, Cs^{137}; Fe, Fe^{55}, Fe^{59}; I, I^{129}, I^{131}, I^{McQ}; Ir, Ir^{204}; K, K^{43}; Li^{8}, Li^{9}; Na, Na^{24}; P, P^{32}; Rb, Rb^{87}; S, S^{35}; Se, Se^{75}; Sr, Sr^{90}; Tl, Tl^{204}. I trust that the facetiousness of my analogy is not misunderstood. Among these elements may be noted I^{129}, I^{131} and the one and only I^{McQ}. We may speculate that our Rocky Mountain boy was a highly receptive element but still somewhat different from either the congenitally endowed or the acquired type. I^{131}, for example, exerts its influence in a single target organ, whereas I^{McQ} possesses that facility of activating diverse human elements unsuspected of having particular potentiality. Many of these in turn have continued the chain reaction. In a routine photograph of the pediatric staff at the University of Minnesota taken in the peaceful nineteen thirties, we find that some 50% of the physicians there are pursuing careers in science and teaching a decade later. The cyclotronic action was unseen and penetration was deep in spite of the thickest of protective coverings. There are no less than two score men who, in part or wholly, have been induced to follow the McQuarrie educational tradition, a dozen of whom occupy positions as heads of departments or the equivalent.

From Utah his adventures took him to Berkeley, Baltimore, Detroit, New Haven, Rochester, and then to Minnesota, where it was their good fortune to benefit from his inspirations for more than a quarter of a century. His odyssey also included Peking, Rome, Tokyo, Rio de Janeiro, and Honolulu, then back to Berkeley and Oakland where he is now settled.

A strong feeling of loyalty has developed and often at meetings such as this, men following the McQuarrie educational tradition gather for mutual stimulation. A particularly memorable occasion was the celebration of his 25th year at Minnesota where several hundred former associates and friends met for three days of scientific-clinical conferences, the proceedings of which resulted in the volume "Essays on Pediatrics."

One of God's gifts to mankind is that energy cannot be destroyed, it can only be transferred from one form to another. In the pediatric world John Howland stands out because of his works and because of his inspiring influence and spirit. Many received direct inspiration from this remarkable person. Today, we are honoring one who, in spite of short exposure, received his full share and practiced the idealism for which Dr. Howland stood. Irvine, all of us, especially those of us who have been activated to live lives beyond our congenitally endowed potentialities are grateful to you. We are happy to have you honored by receiving the medal which was named after the man who influenced you to make this world better and happier, because you have been what you are—an activator.

Children's Hospital, University of Texas School of Medicine, 800 Avenue B, Galveston, Texas.

ACCEPTANCE BY DR. IRVINE McQUARRIE

President Weech, Dr. Hansen, Councilmen, Fellow Members of the American Pediatric Society, and Guests:

It must be all too obvious to you that I am overwhelmed by this manifestation of your good-will and confidence in conferring upon me the coveted John Howland Medal and Award for 1958. The experience of losing my composure and becoming unable to give full and appropriate expression to the mixed feelings of pleasure, gratitude, and humility aroused by the occasion leads me to wonder about the intactness of my own mesencephalic centers, which are alleged to control the affect. Indeed, while my loyal friend and long-time right-hand associate, Dr. Hansen, was speaking his generous words in my behalf, emotional equanimity could be sustained only by voluntarily calling to mind one of Lew Thomas' choicest aphorisms to the effect that "a little flattery won't hurt you if you don't inhale."

In response to being presented with this Medal and Award in previous years, each of my distinguished predecessors has graciously disburdened himself of a veritable diadem of brilliant scientific ideas, bearing upon some special phase of his own research or some reflections on his medical philosophy. These scholarly discourses now adorn the shelves of pediatric libraries everywhere within the English-speaking world and thus memorialize in perpetuity the name of our gifted pediatric colleague, John Howland, whose own professional career exemplified the finest traditions in medical education, scientific research, and pediatric practice.

The promotion of these interrelated professional activities was the primary objective for which the American Pediatric Society was founded approximately seventy years ago. Fortunately, the same high purpose still motivates this organization and the scientific programs of its annual meetings continue to provide an admirable open forum for the presentation of new and imaginative scientific contributions for critical review and stimulating discussion by all of its members and their invited guests. The quality of pediatric education, clinical investigation, and the art of caring for patients have all been influenced immeasurably by this unique society. Its continued success is attributable very largely, I believe, to the liberal eclecticism that actuates its Advisory Council, a rare committee, composed of individualistic younger men and women, who earnestly and constantly strive to maintain the Society's high standards and progressive character. Most of our members must be cognizant of the extent to which the Society has contributed to the advancement of scientific pediatrics throughout the world. The wisdom of insuring its own vigor by broadening the base of requirements for membership is an example of this eclecticism. Selection of new members on the basis of demonstrated competence or achievement in some one or more of the several subspecialty areas within the broad pediatric field, regardless of sex, race, color, creed, academic degree, or special scientific discipline espoused, is highly commendable.

In his laconic official letter notifying me of the Society's action, our amiable Secretary, Dr. McGuinness, gave no information concerning the specific basis on which this year's Award was made, thereby leaving the title of an expected response fatefully up to me and the proverbial "grapevine."

According to the latter source and kindly advice from several old friends, I am expected to venture something in the way of an explanation concerning the predilection for full-time teaching and research careers shown by my pupils and younger asso-

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ciates. Having little ability to deduct abstract principles from chaotic masses of dissimilar data, I find it impossible to formulate a systematic exposition on this topic which could possibly be of help to others with similar problems.

About all that one can say is that genuine scholars seem to be "born" and not "made." The successful teacher does his part when he discovers the potential scholar and then provides adequate incentive for him to develop his own natural capacities through his own enterprise. The most propitious attributes of character and personality in a potential young scholar and leader are intellectual curiosity, idealism, inspirability, discernment, imaginativeness, zeal for learning and willingness to work, perseverance, optimism, imperturbability, and magnanimity. In further pursuit of Dr. Hansen's facetious simile of the old miner from the West searching for "streaks of gold," we may compare the responsible head of a clinical department with the old prospector. In his quest, if he discovers a candidate possessed of such qualities of character as these, he is truly the "lucky prospector."

The teacher's recollections of his own experience as a student often determine his attitude. It may be justifiable to reminisce briefly to illustrate some of these points. My own tardy awakening to the satisfactions inherent in the scholarly life came near the end of the second year of basic science study at the University of California in Berkeley. This was greatly intensified during the two additional years of work at the Hooper Foundation for Medical Research in San Francisco. How fortunate I was as a student to have had as medical teachers such stimulating and inspiring men as H. M. Evans, G. W. Corner, and P. E. Smith in Anatomy, F. P. Gay in Bacteriology and Immunology, and T. B. Robertson in Biochemistry. The climax of my exhilaration was reached after my arrival on the other side of the San Francisco Bay to work with a genuine master of the art of teachership-by-example, George H. Whipple. Despite the fact that the United States was still engaged in the First World War at the time, with all of its distractions and enforced austerities at home, those two years in the atmosphere of the research laboratory under the encouraging tutelage of a friendly and understanding mentor were among the happiest days of my entire life.

The personal examples of these scholarly teachers at California led me to seek admission with advanced standing to the Johns Hopkins Medical School for clinical study and training during my last two years. There I hoped to find in clinical medicine an atmosphere as congenial and rewarding from the scientific viewpoint as California had been during my first three and one-half years in the basic science fields. Drs. Whipple and Evans aided and abetted this plan to transfer to Hopkins, where both had previously held associate professorships in their respective fields, Whipple in Pathology with Welch and Evans in Anatomy with Mall.

I transferred to Baltimore in June, 1919. During the summer of that year, acquaintance was made with a number of brilliant younger men, who were teaching clinical surgery and medicine on a full-time scientific basis. In the Pediatric Department, Drs. Howland, Park, Shipley, Gamble, Powers, Kramer, Shohl, Ross, and Tisdall were all doing interesting research work at the time. Many of the clinical teachers were working on problems with techniques similar to those we had used in animal research at the Hooper Foundation laboratories. After attending the senior Diagnostic Clinics conducted in the old Harriet Lane amphitheatre by Dr. Howland, making weekly ward rounds with Drs. Park and Powers, and listening to a short series of lucid lectures on infant metabolism and nutrition by Gamble, I knew that pediatrics was my choice of clinical fields. An internship in this discipline immediately following graduation was a financial impossibility, but the hope of returning to it at some time in the future remained uppermost in my mind. Dr.

Howland at that time impressed me as being the sharpest and most adroit diagnostician among the brilliant chiefs of the clinical services at the Johns Hopkins Hospital, but he seemed to be unnecessarily austere and unapproachable. Fortunately, Drs. Park [1] and Gamble [2] have subsequently succeeded in correcting this erroneous impression and in presenting him to medical posterity in a much warmer and more admirable light.

In January, 1924, after I had been in charge of the Division of Metabolism and Endocrinology at the Henry Ford Hospital for nearly two years, a situation arose which made it possible for me to choose between remaining in the field of internal medicine or preparing to return to pediatrics. The Henry Ford Hospital, whose governing Board had decided to develop a special division of Pediatrics, offered me a full year's leave on salary to study pediatrics at any place of my choice in America to prepare further for full-time work in that field. After visiting several outstanding teaching centers elsewhere, I sought advice from Dr. Park in New Haven. He had been called there from Baltimore in 1921 to develop a new Department of Pediatrics at Yale on the full-time plan. He had taken Drs. Powers and Shohl with him from Baltimore to strengthen the clinical teaching and laboratory research functions. Soon thereafter, he had added Dr. Ethel Dunham to take charge of the Out-Patient Department. Dr. Martha Eliot, who had previously served as clinical resident both on Dr. Marriott's Service in St. Louis and on the Service at New Haven, joined Dr. Park in his comprehensive investigation of the problem of rickets. This study provided a superb opportunity to observe a well-planned clinical research project at close range during the remainder of that year.

To this audience with so many of his old pupils and associates present, it is quite superfluous to emphasize the extent to which Dr. Park's direct influence contributed to my becoming established in the pediatric field. Through informal conversations carried on with him during long hikes in the woods and hills around New Haven one was bound to acquire a lot of exact knowledge and Parksian philosophy. Similar associations with Dr. George Whipple, both before and after this period, first at the Hooper Foundation and later at the University of Rochester, were likewise invaluable. The immense inspiration and intellectual stimulation that was derived from association with these two stalwarts, themselves fast friends and summer fishing companions, constitute the highlight of my career as a student.

The purpose of relating these reminiscences is to emphasize the conviction that friendly examples, involving teachers and their pupils, are most potent influences, which may be carried on as traditions from one generation to the next. Because of the immense personal benefit derived from such happy relationships in academic life, the desire to share experiences with my close associates has been impelling. Giving them positive encouragement to follow scholarly pursuits while maintaining broad clinical interests and proper balance between the different facets of the academic career has been extremely rewarding. Medical research, my favorite diversion, is fun, and team research can be just as rewarding as individual experimental work when there is proper understanding between the interested parties.

The added stimulation and satisfaction that one usually derives from independent thinking and investigation must be encouraged too, because such identification with one's own original work may be essential to growth of a person's independent status and personal dignity. The established head of a University Department, being genuinely interested in both the advancement of scientific knowledge and the unhampered growth of younger colleagues, learns to derive most of his personal satisfaction in life from observing their achievement. It seems to me to be important to take a friendly and sympathetic attitude toward their domestic, financial, and other

extracurricular problems, without seeming to be unduly concerned or meddlesome. It is not unnatural for a proud and well-wishing "chief" to commend his younger colleagues from time to time on their meritorious performances, whether these are achievement in teaching, clinical investigative work, skill in caring for patients, or presentation of exciting new scientific reports before appreciative audiences. A successful leader or teacher of younger associates makes every effort to avoid the development of jealousies and selfishness among them. He should exercise extreme patience and always do his utmost to avoid the use of sarcasm, which sensitive people abhor as a viperous idea-blocking invention of "Old Nick."

In concluding this rambling discourse, I would be remiss, indeed, were I not to acknowledge with profound gratitude the preponderant part that my former colleagues have always played in the development and the smooth running of our happy Department of Pediatrics at the University of Minnesota. Finally, Dr. Hansen, I want to thank you again for your gracious recognition of the essential role played by my "coenzyme," Mrs. McQuarrie.

Children's Hospital of the East Bay, Oakland 9, Calif.

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Transactions of the American Pediatric Society

Sixty-Eighth Annual Meeting

DR. A. ASHLEY WEECH, President; DR. ALTON GOLDBLOOM, Vice-President; DR. AIMS C. McGUINNESS, Secretary-Treasurer; DR. STEWART H. CLIFFORD, Recorder-Editor; DR. JOHN A. ANDERSON, Chairman of the Council

Atlantic City, N. J., May 8-9, 1958

SCIENTIFIC PROGRAM

1. **Infectivity of Ribonucleic Acid of Poliovirus on HeLa Cell Monolayers**
   Hattie E. Alexander, M.D.; Gebhard Koch, M.D.*; Isabel Morgan Mountain, Ph.D.*; Katherine Sprunt, M.D.,* and Olga Van Damme, M.A.*
2. **An Epidemic of Aseptic Meningitis Attributable to Coxsackie B5 Virus**
   Edward C. Curnen, M.D.; Arthur H. London Jr., M.D.*; Eru Tanabe, B.S.*; W. Paul Glezen, M.D., and Jacob Koomen, M.D.*
3. **The Use of Bacitracin in the Treatment of Overwhelming Staphylococcal Infections**
   Hope Craig Perry, M.D.*; Roger H. Perry, M.D.*; Charles H. Bauer, M.D.*; Olga Kocevalov, M.D.,* and Heinz F. Eichenwald, M.D.*
4. **Early Ambulation in Rheumatic Fever**
   Matthew L. Gibson, M.D.,* and G. Robert Fisher, M.D.*
5. **The Course of Acute Nephritis in Children Allowed Early Resumption of Normal Physical Activity**
   Wallace W. McCrory, M.D.; Daniel Fleisher, M.D.,* and William B. Sohn, M.D.*
6. **Studies of Insensible Weight Loss, Clinical and Experimental**
   George M. Guest, M.D.; Mary D. Pettit, R.N.*; Carlos Araujo, M.D.*; James Frid, M.D.*; Bernard Combes, M.D.*; C. deMenibus, M.D.,* and Eva Wittgenstein *
7. **Disturbances of Acid-Base Equilibrium in Salicylate Intoxication**
   Robert W. Winters, M.D.,* and Nelson K. Ordway, M.D.
8. **Experimental Water Intoxication**
   John D. Crawford, M.D.; Philip R. Dodge, M.D.,* and Jan H. Probst, M.D.*
9. **Effects of Acute Changes in Extracellular Fluid Composition on Bone Sodium Content**
   Gilbert B. Forbes, M.D., and Richard B. Tobin, M.D.*
10. **Hyperkalemic Periodic Paralysis**
    Thomas Egan, M.D., and R. Klein, M.D.
11. **The Syndrome of Infantile Nephrosis**
    Howard G. Worthen, M.D.*; Robert L. Vernier, M.D.,* and Robert A. Good, M.D.
12. **Congenital Renal Tubular Acidosis**
    Harold E. Harrison, M.D.; J. Julian Chisolm Jr., M.D.,* and Helen C. Harrison, Ph.D.*
13. **A Study of the Spectrum and Genetics of Nephrogenic Diabetes Insipidus**
    S. A. Kaplan, M.D.*; A. Yuceoglu, M.D.,* and J. Strauss, M.D.*
14. **Renal Conservation of Base by Infants Fed Human Milk and Whole Cows' Milk**
    Samuel J. Fomon, M.D.*; Dorris M. Harris, M.D.,* and Robert L. Jensen, B.S.*
15. **Skeletal Maturation and Dental Development**
    Richard Wagner, M.D., and M. Michael Cohen, D.M.D.*
16. **Diagnosis of Collection of Subdural Fluid by Transillumination**
    Frederick A. Horner, M.D.*; N. C. Webb Jr., M.D.,* and Keasley Welch, M.D.*
17. **Cineangiocardiography in the Study of Pulmonic Stenosis**
    F. N. Silverman, M.D.; S. Kaplan, M.D.*; E. Matthews, M.D.*; K. Edwards, M.D.,* and G. Currarino, M.D.*
18. **Repeated Plasmapheresis in the Immunized and Convalescent Donor**
    Joseph Smolens, B.S.*; Joseph Stokes Jr., M.D.; Agnes B. Vogt, Ph.D.,* and Mary N. Crawford, M.D.*
19. **Hereditary Enzymatic Defects as Illustrated by Hypophosphatasia**

* By invitation.

Norman Kretchmer, M.D., Ph.D.*; Michael Stone,* and Charles Bauer, M.D.*

20. **Erythrocyte Phosphate Metabolism in Infancy**
Alvin Zipursky, B.Sc., M.D.*

21. **Pseudo-Pseudo-Hypoparathyroidism as an Allelic Form of Pseudo-Hypoparathyroidism: Report of the Youngest Case, with Description of a Diagnostic Screening Technique**
Esten W. Ray, M.D.* and Lytt I. Gardner, M.D.

22. **Aldosteronism and Hypertension: The Influence of Complete Adrenalectomy upon Essential Hypertension in a Child**
R. J. Slater, M.D.*; D. W. Geiger, M.D.*; J. Leeson,* and A. G. Gornall, Pr.D.*

23. **Effects of Drugs on Experimental Febrile Seizures: Development of a New Specific Therapy**
J. Gordon Millichap, M.D.*

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Forrest H. Adams, M.D.; Petter Karlberg, M.D.,* and John Lind, M.D.*

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B. M. Gasul, M.D.*; E. H. Fell, M.D.*; M. Moreano, M.D.*; M. Weinberg Jr., M.D.,* and A. Gordon, M.D.*

26. **A New Inborn Error of Fatty Acid Metabolism**
John A. Bigler, M.D.; Roland Mais, M.S.,* and David Yi-Yung Hsia, M.D.*

27. **Chronic Renal Disease in Children with Lipodystrophy**
Sydney S. Gellis, M.D.; Sidney Green, M.D.,* and Douglas Walker, M.D.*

28. **The Metabolism of Substance S in Children and Adults**
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Herbert A. Wenner, M.D.; T. D. Y Chin, M.D.,* and Alice Marsh, M.D.*

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Lawrence M. Bugbee, M.D.*; Robert B. Stewart, Ph.D.,* and Arthur A. Like, M.D.*

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Samuel Karelitz, M.D., and Henry D. Isenberg, B.S., M.A.*

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Maxwell Stillerman, M.D.,* and Stanley H. Bernstein, M.D.*

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Walter Heymann, M.D., and Sydney G. F. Wilson, M.B., M.R.C.P.

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Saul Krugman, M.D.*; Robert Ward, M.D.; Joan P. Giles, M.D.; A. Milton Jacobs, M.D.,* and Oscar Bodansky, M.D.*

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Edith M. Lincoln, M.D., and Amparo C. Adiao, M.D.*

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Alex J. Steigman, M.D.; Murray M. Lipton, Ph.D.,* and Edwin Ranzenhofer, M.D.*

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L. S. Baur, Ph.D.,* and L. J. Filer Jr., Ph.D., M.D.*

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L. Fischer, Ph.D.*; W. Oppel, M.S.*; H. Knobloch, M.D.*; R. Rider, Sc.D.,* and P. Harper, M.D.

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W. Oppel, M.S.*; R. Rider, Sc.D.*; L. Fischer, Ph.D.*; H. Knobloch, M.D.,* and P. Harper, M.D.

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George R. De Muth, M.D.*; David G. Dickinson, M.D.,* and James L. Wilson, M.D.

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Ruth Whittemore, M.D.*

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Harold H. Gunson, M.B., Ch.B.*

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Myron E. Wegman, M.D., and James G. Hughes, M.D.

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65. **Immunization with Orally Administered Attenuated Live-Virus Poliomyelitis Vaccine**
Mauricio Martins da Silva, M.D.*; John L. McKelvey, M.D.*; Konald A. Prem, M.D.*; Eugene A. Johnson, Ph.D.,* and Herald R. Cox, Sc.D.*

66. **Male Pseudohermaphroditism in Three Siblings**
Charles H. Bauer, M.D.*; Myron Winick, M.D.*; Lewis Arnow, M.D.*; Donald

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P. Beirne, M.D.,* and Norman Kretchmer, M.D., Ph.D.*

67. **Obligatory Renal Water Requirements in Infants Fed Varying Formulae**
Philip L. Calcagno, M.D.*; P. K. Mukherji, M.D.,* and Mitchell I. Rubin, M.D.

68. **Pulmonary Complications of Congenital Heart Disease in Infants**
Edward C. Lambert, M.D.*; Y. Ramon Perez, M.D.,* and Peter Vlad, M.D.*

69. **Wilson's Disease Without Neurological Manifestations: An Unsuspected Cause of Cirrhosis in Children**
Andrew Sass-Kortsak, M.D.*; Morris Cherniak, M.D.,* and Mary Louise Hose, B.A.*

70. **The Pattern of Folic Acid Deficiency Development During Folic Acid Antagonist Therapy in Children with Acute Leukemia and Neuroblastoma**
A. Leonard Luhby, M.D.*; Jack M. Cooperman, Ph.D.*; David N. Teller, B.S.*; Jeffrey B. Wenig, B.S.,* and Robert Feldman, M.D.*

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Julius B. Richmond, M.D., and Leonard Hersher, Ph.D.*

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Doman Keele, M.D.*; Malcolm Holliday, M.D.,* and Thomas Egan, M.D.*

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Donald V. Eitzman, M.D.,* and Richard T. Smith, M.D.*

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Wm. A. Reilly, M.D.; K. G. Scott, Ph.D.*; G. L. Searle, Ph.D.,* and J. N. Castle, A.B.*

76. **Observations on High and Low Protein Diets**
Selma E. Snyderman, M.D.*; Audrey Boyer*; Maurice Kogut, M.D.,* and L. Emmett Holt Jr., M.D.

77. **The Plasma Osmolar Concentration in Premature Infants**
Hans. G. Keitel, M.D.*

78. **Hemoglobin and Serum Iron of Infants Fed Milk Mixtures With and Without Added Iron**
A. Marsh, M.D.*; H. Long *; and E. Stierwalt, R.N.*

79. **Prognosis for Prematures During Infancy**
William T. Newsom,* and Louise Pesut *

80. **Mode of Transmission of Familial Ectodermal Dysplasia**
Allen H. Kline, M.D.*; J. B. Sidbury Jr., M.D.*; C. P. Richter, M.D.,* and J. Billingsly, M.D.*

81. **Female Pseudohermaphroditism Associated with Cystic Ovaries Containing Luteinized Thecal Cells: A Review of Four Cases**
John F. Crigler Jr., M.D.,* and John M. Craig, M.D.*

1. **Infectivity of Ribonucleic Acid of Poliovirus on HeLa Cell Monolayers.** HATTIE E. ALEXANDER, M.D.; GEBHARD KOCH, M.D.*; ISABEL MORGAN MOUNTAIN, Ph.D.*; KATHERINE SPRUNT, M.D.,* and OLGA VAN DAMME, M.A.* The Babies Hospital (Presbyterian Hospital) and the Department of Pediatrics, Columbia University, College of Physicians and Surgeons, New York.

The results of the experiments to be described suggest that they offer another example of the principle that in certain animal, as well as plant viruses, ribonucleic acid (RNA) may function either as a heredity determinant or as an infectious agent, depending upon the host cell and the environment. In 1956, Gierer and Schramm reported that the RNA extracted from tobacco mosaic virus is itself infectious on tobacco leaves (Gierer, A., and Schramm, G.: *Z. Naturforsch* 11b:138-142, 1956).

This report describes the reproducible infectivity on HeLa cell monolayers of RNA extracted by 80% phenol from Type I and Type II polioviruses, grown in human amnion cells in tissue culture, and purified and concentrated 100 times. The infectivity was shown to be due to the RNA itself, and not to the whole virus, by a comparison of the inactivating capacity of various test substances on infectious whole virus and infectious RNA. The table shows the results of this comparison.

Substance Tested for Inactivation	Inactivation of Whole Virus	Infectivity of Infectious RNA
RNAase 100 μg/ml	0	+
DNAase 100 μg/ml	0	0
Chymotrypsin 100 μg/ml	0	0
Papain 100 μg/ml	0	0
Immune Monkey Euglobulin 1:10	+	0
Normal Monkey Euglobulin 1:10	0	0
Whole Normal Monkey Serum 1:10	0	+

* By Invitation.

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It is seen that ribonuclease which has no effect on whole virus can completely inactivate infectious RNA. Desoxyribonuclease (DNAase), on the other hand, has no effect on either. The latter fact makes it possible for the first time to eliminate the possibility that the trace of DNA, found in purified poliovirus, can be the heredity determinant. Proteolytic enzymes are also without effect on either. Homotypic immune euglobulin which can completely neutralize the whole virus cannot prevent the infectivity of the RNA.

The results suggest that the inactivation of infectivity of RNA by whole normal monkey serum is due to the content of RNAase which could not be demonstrated in euglobulins.

After invasion of HeLa cells by the RNA, the cell is directed not only to the replication of the RNA, but also induced to produce the specific protein needed for production of whole virus of the type of origin of the RNA.

Discussion

DR. ALBERT B. SABIN, Cincinnati: The work of Dr. Alexander and her associates in more extensive experiments than she has had time to present here has established, I think beyond doubt, that the RNA (ribonucleic acid) portion of poliomyelitis virus is responsible for doing the "dirty work" of the virus. The question that I would like to raise here—there are many questions that are raised as a result of this work—is: what is the effect of this newer knowledge of how the virus behaves in a single cell on our understanding of a disease process in which many cells must be affected in order for disease to be produced? The very fact that a culture of poliovirus, representing virus that came out of the cells, loses none of its infectivity after treatment with ribonuclease means that what comes out of the cell is not raw ribonucleic acid but a more highly organized virus particle that is much better equipped for invading cells. I would like to ask Dr. Alexander whether there is any indication that our old concept of how a tissue is affected by viruses, i. e., that mature virus comes out from one cell and then infects many other cells around it, has to be modified in any way by the new evidence that specific antibody which acts on the complete mature virus particle has no effect on the RNA of the virus which actually initiates the infectious process in the cell. Is it possible that the RNA can move from cell to cell without coming out into the open as a complete virus particle susceptible to antibody?

DR. LEWIS WANNAMAKER, University of Minnesota, Minneapolis: I would like to add my admiration of this beautiful work of Dr. Alexander. I have one question in regard to these experiments. Will heated whole monkey serum inactivate the infectivity of RNA? I ask this question because most mammalian sera contain DNAase as well as RNAse. The former enzyme is more heat labile and probably would be destroyed, whereas the RNAase in most cases would still be active after heating.

DR. ALEXANDER: The question which has been raised by Dr. Sabin is a fascinating one, but one to which he knows I do not have the answer. Dr. Wannamaker, we have done some very limited experiments on the effect of heat on the whole normal monkey serum which suggests that the RNA inactivating effect is greatly reduced when enough heat is applied. However the RNAase is so resistant that the required heat coagulates the protein, so we doubt that our experiments answer this question. On the other hand, it is well known, as you implied, that ribonuclease is very resistant to heat, and it really requires enough heat to coagulate the protein even to anticipate any change in its action.

2. An Epidemic of Aseptic Meningitis Attributable to Coxsackie B5 Virus. EDWARD C. CURNEN, M.D.; ARTHUR H. LONDON JR., M.D.*; ERU TANABE, B.S.*; W. PAUL GLEZEN, M.D., USPHS(CDC),* and JACOB KOOMEN, M.D.* Department of Pediatrics, University of North Carolina School of Medicine, Chapel Hill, N. C., and the Division of Epidemiology, North Carolina State Board of Health, Raleigh, N. C.

In 1957, cases of poliomyelitis reported from North Carolina totaled only 233, the lowest number since 1949. Eighty-three or approximately one-third came from Durham County; of these only 2 were considered paralytic and none died. More than half had previously received poliomyelitis vaccine.

An investigation of hospitalized patients from Durham County and surrounding areas was initiated in July. In August it was established that many of the patients reported as cases of nonparalytic poliomyelitis were infected with strains of Coxsackie virus B5. During August and September the investigation was extended to survey the occurrence of this infection in the families of hospitalized patients and the incidence of concurrent illness in the city of Durham.

Coxsackie virus B5, the predominant viral agent encountered, was recovered in cultures of monkey kidney cells from 96 to 227 patients with aseptic meningitis who were studied. The recovery of 137 strains from these 96 patients indicates that in many instances the virus was obtained from multiple sources. Eighty strains were from stools and nineteen, from pharyngeal swabbings. In 38 patients the virus was detected in cerebrospinal fluid. Serologic evidence of infection with Coxsackie

* By invitation.

virus B5 was found in all patients adequately tested among the 96 with meningitis from whom this virus was recovered and in 26 additional patients. During 1957, enteroviruses other than Coxsackie B5 were detected in only seven patients with aseptic meningitis. They included Coxsackie A9 in one and Coxsackie B4 and ECHO Type 4 viruses each in three patients. Poliovirus was not recovered from any of the patients with aseptic meningitis including those reported as nonparalytic poliomyelitis.

In patients with meningitis attributable to Coxsackie virus B5 the clinical picture was characterized by fever, severe headache, nausea and vomiting, malaise of varying intensity, and absence of paralysis or altered reflexes. Pleurodynia was rare and skin rash was not a feature. The course was frequently biphasic and usually uncomplicated. Clinical laboratory data showed no consistent or significant abnormality other than pleocytosis of the cerebrospinal fluid which ranged from a few cells to more than 2000, usually with an appreciable percentage of polymorphonuclear forms.

In August it was decided to study the distribution of viral infection in 32 families of 35 representative patients with aseptic meningitis. Two cases of meningitis occurred in each of three families. Coxsackie virus B5 was recovered from 20 of the patients with meningitis and not recovered from 13 others who were tested. In none of these patients was a viral agent other than Coxsackie B5 encountered. The 32 families studied included 173 members. Coxsackie virus B5 was recovered from a total of 56 members in 26 families and serologic evidence of infection by the virus was found in members of three additional families. Poliovirus Type 3 was found in a specimen of feces from an infant in one household.

Evidence from the community survey indicated that approximately 10,000 inhabitants of the Durham area had acute illness during the epidemic period. The recovery of Coxsackie virus B5 from patients who had meningitis in a total of 14 counties indicated that this viral infection and associated disease were widely distributed in central and eastern North Carolina during the summer of 1957, when infection with poliovirus was notably infrequent.

Discussion

Dr. Albert B. Sabin, Cincinnati: I think that Dr. Curnen's contribution should not go without some comments on its significance. Every summer pediatricians are faced with thousands of febrile illnesses, and the problem of their etiology has only just begun to be resolved. It is being resolved by studies performed by teams such as Dr. Curnen and his associates, i. e., by people who have both the ability to differentiate clinical manifestations and the ability and facilities to associate them with specific agents. Please remember that Coxsackie B5 represents only one of more than 50 known viruses that may compete for the intestinal tract of children and their parents during the summer period. It is one of the interesting epidemiologic manifestations that in one particular area one of these viruses can get the inside track and somehow push most of the others off. In other areas last summer, it was ECHO 9 which took over and pushed most of the others off the track. Of special interest is the question of what was going on in the community at the time Dr. Curnen saw these patients in the hospital. In other words, for every patient admitted to the hospital, how many were sick in the community with Coxsackie B5? How many were infected without being sick? Information on that has already been accumulated on other enteroviruses. For example, last year in Milwaukee we were able to show that for every patient in the hospital with ECHO 9 virus disease, there were 200 sick at home, and that 85% of all the infections with this virus caused illness. What was the situation in relation to Coxsackie B5, Dr. Curnen?

Dr. Heinz F. Eichenwald, New York: I would like to ask Dr. Curnen a question which perhaps is an extension of Dr. Sabin's remarks. Could he tell us whether the ratio of clinical illness to inapparent infection with Coxsackie B5 virus varied with age?

Dr. Joseph Stokes Jr., Philadelphia: Could Dr. Curnen give us information concerning the serological tests conducted in other areas which would indicate perhaps whether there has been an extensive seeding of such virus in the population? I believe he noted that the incidence in Negroes was lower. Would this indicate that there was already a seeding in this part of the population because of poor sanitation?

Dr. Edward C. Curnen: Studies made in 32 families of patients with aseptic meningitis revealed the presence of infection by B5 Coxsackie virus in a total of 29 families in an average of approximately two members per family. Virus was recovered and serologic evidence of infection was demonstrated not only in the 35 patients with meningitis but also in members with mild illnesses and in others with no disease. Coincident with the epidemic of aseptic meningitis it was noted by practicing physicians that there was considerable nonspecific febrile illness in Durham. In order to study this, a house-to-house survey was made. A sample population was selected by picking at random 23 of the 1100 blocks in the city. Three hundred and twenty-seven families were interviewed. Fifty-nine or 18% of the households were found to be represented by at least one person

with illness. Illnesses occurred in 21% of the white and in only 10% of the nonwhite families.

The 327 families included 1091 persons: of these, 99 gave a history of illness. This represents an attack rate of 9%. On this basis it was estimated that approximately 10,000 people were clinically ill in Durham County during the outbreak in which 104 patients with aseptic meningitis were encountered. In answer to Dr. Eichenwald's question about the age incidence of infection, we found that the attack rate was highest in young children and progressively decreased with age. Aseptic meningitis occurred in both children and adults. The spread of infection within families appeared to be rapid. Serologic evidence supported other indications that infection with Coxsackie B5 virus was prevalent in the community. We were not able to obtain extensive serologic data from the Negro sections of the community, but the attack rate of mild illness in the nonwhite part of the population was certainly less than that in the white members of the community. This distribution paralleled that of aseptic meningitis. We do not have evidence to account for the observed difference in incidence according to race. In the course of studies beginning in 1953 we had not previously encountered the Coxsackie B5 virus until 1956 when a strain was recovered from one patient. The epidemic of aseptic meningitis during the summer of 1957 in Durham represented, as best we could determine, a new experience in that area.

3. The Use of Bacitracin in the Treatment of Overwhelming Staphylococcal Infections. HOPE CRAIG PERRY, M.D.*; ROGER H. PERRY, M.D.*; CHARLES H. BAUER, M.D.*; OLGA KOCEVALOV, M.D.,* and HEINZ F. EICHENWALD, M.D.,* Department of Pediatrics, the New York Hospital and the Cornell Medical Center. Introduced by S. Z. Levine, M.D.

The increasing incidence of severe staphylococcal infection during the neonatal period appears to be directly related to the wide dissemination of the "epidemic" phage Type 80/81. This particular type has been the cause of most recent nursery epidemics of staphylococcal disease.

The problems represented by these infections are compounded by the fact that many strains of this phage type are unusually resistant to the commonly employed antimicrobial agents.

The present study reports the results of combined therapy with bacitracin and penicillin in 17 infants critically ill with staphylococcal sepsis or penumonia with empyema. All had received other antimicrobial agents previously but had continued to pursue a rapid down-hill course.

The bacitracin was administered for 5 to 7 days in a dose of 1000 units per kilogram per day given intramuscularly in divided doses. This drug was chosen as the primary therapeutic agent in these particular patients because (1) susceptibility tests had shown these strains of staphylococci to be highly resistant to all other available antimicrobial agents with the exception of novobiocin, oleandomycin, and, in a few cases, erythromycin, and (2) the patient's clinical condition was sufficiently poor that a more rapidly acting agent than the latter three drugs seemed essential.

Seventeen critically ill infants were treated with this regimen, followed by a supplementary course of another antibiotic to which the staphylococcus was susceptible. Sixteen patients survived, with a beneficial clinical response generally occurring promptly after initiation of therapy. The renal toxicity of bacitracin was found to be slight and transient in nature.

Discussion

DR. WILLIAM L. BRADFORD, Rochester, N. Y.: The selection of this paper for presentation is obviously justified by the current importance of the subject and the material just presented. Unlike certain viruses that coexist such as the poliomyelitis and Coxsackie agents, I understand that a certain phage type of staphylococcus tends to dominate the nasal flora especially during an outbreak. Also there is evidence that certain individuals become carriers while others do not. These findings, if true, suggest a strong factor of local immunity. I wonder if Dr. Perry would care to comment on this.

DR. ROLAND B. SCOTT, Washington, D. C.: In view of the present availability of Ristocetin, I would like to know if the authors have had an opportunity to test the in vitro sensitivity of the strains of staphylococci encountered in their study to this newer antibiotic. It is my impression that Ristocetin is probably more effective in the treatment of severe staphylococcal infections and is also less nephrotoxic than parenterally administered bacitracin.

DR. RICHARD SMITH, Dallas, Texas: I think that it is evident to all those taking care of any number of these patients that these are the best recovery data that have been presented by anybody, certainly far superior to ours. I note that a majority of patients treated in the latter part of the series received novobiocin for as long as 42 days. Our own experience demonstrates that this has been an effective drug alone when used early. However, the risk of using bacitracin, in view of the data presented, certainly seems acceptable in these extremely ill infants, and it allows us the use of this otherwise risky antibiotic. On the other hand, I hope bacitracin will not be used unnecessarily because of these data, since frequent

* By invitation.

usage in a hospital is associated with rapid development of resistant strains.

DR. ALLAN M. BUTLER, Boston: I would like to say one word in terms of the care necessary in using a drug having this kind of toxic effect. If I remember correctly, 1000 units per kilogram per day were used in these neonates. Excellent data on the toxicity of drugs since the beginning of this century indicate that, except as diminished renal function and elimination of drug increased the effective dose in these neonates, prescription of the appropriate per kilogram dose for an infant may well be toxic for the older child, whereas dosage per square meter is appropriate regardless of age of patient.

DR. T. A. GOOD, Baltimore: I wanted to comment on the use of a specific antibiotic in such cases as this. About four years ago, we managed an epidemic of neonatal sepsis at Salt Lake City in which the decision to use a specific antibiotic agent, erythromycin, was made rather late. This was because of ignorance, particularly concerning the sensitivities of the particular strain of staphylococcus we were dealing with. Consequently, we had patients whom we treated rather late in the course of their disease. Subsequently, we were able to treat about 20 patients early. The recovery, of course, in the early treated patients was much better than in the late-treated patients. The particular problem dealt with in the paper presented is that they have used two agents which are toxic drugs. Novobiocin has been noted for toxicity, particularly in the newborn, and bacitracin in addition is known to have toxic qualities when given systemically. I just wanted to say, therefore, that the decision must be made to use a specific drug early, even if it is toxic. The recognition of the sensitivity of staphylococcus you are dealing with is extremely important. This has been emphasized particularly by Edmunds and Farquahar in 1952. We must know constantly in all of our hospitals what type of staphylococi we are dealing with, so that we are able to treat specifically early, even if it means a toxic drug. In late stages the treatment of staphylococcal disease, like tuberculosis, is not nearly as rewarding as it is when initiated early.

DR. ELI GOLD, Cleveland: When you are dealing with sick children it may be necessary to use potentially dangerous drugs. However, we ought to give some attention to an over-all plan when employing antibiotics so that the hospital staphylococci do not become resistant to all available antibiotics, thus leading to a desperate search for new ones. It has been the plan in Cleveland to restrict the use of antibiotics on the clinical service to a few drugs: the rest are held in reserve to be used only with the consent of the hospital Infection Committee. This plan has not been in use long enough to comment on its success, but the theoretical advantages are obvious.

DR. BENJAMIN KRAMER, Brooklyn: I wonder how long the antibiotic therapy should be continued and what are the indications for its discontinuance?

DR. JOSEPH STOKES JR., Philadelphia: I have one brief point concerning this very interesting paper. This last winter has seen in certain instances a combining of activity of the staphylococcus and Asian epidemic influenza virus in severe respiratory infections. Nothing was mentioned, as I recollect, about the question of whether the influenza virus was present in the patient that died. I should also like an opinion from the authors as to whether the staphylococcus has been present, in their experience, in the other infants and children when Asian influenza has been present, and what the relationship might have been.

DR. REGINALD A. WILSON, Vancouver, B. C.: We have found the use of bacitracin excellent in staphyococcal pneumonia, and we use it intrapleurally in patients with empyema due to this organism. In view of the recent reports from England (Gould, J. C.: *Lancet* 1:489 (March 8) 1958) that penicillin resistance is aquired in hospitals through a sort of "penicillin fall-out" from the use of the drug indiscriminately and by lack of care when filling syringes, I think it is wise for us to remember that we may do the same thing to bacitracin. Heretofore, bacitracin has retained its potency particularly because intramuscular administration has limited its use. If we use it intrapleurally, we must resolve to be very careful about its dispersal in the air of the hospital wards.

DR. HOPE CRAIG PERRY: In reply to Dr. Bradford, we have no data about local immunity. We have been doing disk sensitivity tests with ristocetin. This organism is sensitive to ristocetin in vitro. However, ristocetin is a more slowly acting drug, and we have felt that time was of the essence in treating these patients. We have treated two older children, aged 6 and 8, with bacitracin. One of these had albuminuria while on bacitracin. It disappeared within the following week. The other had no urinary abnormalities whatever. Both received bacitracin in a dose of 1000 units per kilogram. The use of bacitracin is restricted at present in our hospital. It is available only on consultation, and is not used routinely by any means. Studies for influenza were made in the fatal case, and studies for antibodies were made with several other patients. No evidence of influenza was obtained. By and large, these cases occurred after the epidemic wave of influenza had passed through New York. In reply to the questions about administration, the bacitracin was given in a dose of 1000 units per kilogram per day. It was given deeply intramuscularly in divided doses every six

hours for five to seven days. Penicillin was given at another site.

4. Early Ambulation in Rheumatic Fever. MATTHEW L. GIBSON, M.D.,* and G. ROBERT FISHER, M.D.,* Denver. Introduced by Henry K. Silver.

Bed rest has always been considered to be an integral part of the therapy of rheumatic fever and has been prescribed for variable periods of time regardless of the type of 'specific' therapy that was used. We wish to report our studies at the University of Colorado Medical Center on a group of children with their first attack of acute rheumatic fever who were permitted to be ambulatory within the first few days after admission to the hospital. The children were treated with cortisone, 3 mg. per pound per day orally and were maintained on this dose until all clinical and laboratory evidence of disease activity had disappeared for one week. Particular reliance in assaying activity was placed on the level of serum mucoproteins. The dosage of cortisone was then reduced stepwise by increments of 50 mg. daily at weekly intervals until the children were receiving 100 mg. per day. Further stepwise reductions were carried out at weekly intervals at the rate of 25 mg. daily until the drug was discontinued. If any clinical or laboratory evidence of activity became evident while the drug was being reduced, it was increased to the last preceding dose and maintained at this level until the abnormal findings had disappeared.

In this study 49 consecutive children with their first attack of rheumatic fever (44 of whom had active carditis) were permitted to be up and around and have full freedom on the ward as soon as they were well enough for such activity. This usually took place within 48 hours after admission. Of this group only 1 child has residual heart disease (Grade II MI). Prior to the initiation of this study 22 consecutive children were treated with the same dosage schedule of cortisone but were kept at bed rest for approximately three months. None of these children have residual carditis.

Children who did not have heart disease after their first attack of rheumatic fever, but subsequently had one or more recurrences of activity, were treated by the same regime with cortisone and full activity and they do not have any residual heart disease.

Discussion

DR. R. JAMES MCKAY JR., Burlington, VT.: Particularly since the advent of steroid therapy for rheumatic fever, we who treat rheumatic fever have been guilty of producing iatrogenic psychosomatic disease by keeping these patients at bed rest too long. We have had somewhat similar experiences to the Colorado group, although we have used a different regimen of cortisone treatment. We have also used a slightly different regimen of early ambulation. I can summarize the latter by saying that most of our patients are back in school on full activity within two months of treatment.

DR. ALBERT DORFMAN, Chicago: Would Dr. Gibson say a little more about the selection of patients for this study? I am impressed more by the low incidence of heart disease in both groups than by the difference between them. Ordinarily one sees a very much larger number of patients with fairly severe heart disease, murmurs of considerable significance, which I think rarely disappear this readily, irrespective of type of treatment.

DR. MARGARET H. D. SMITH, New York: I think that early ambulation tends to avoid the iatrogenic psychiatric disturbances, which is very worth while. In the case of tuberculosis, it has been very well shown, I think, in at least two series of well-controlled studies on pulmonary tuberculosis in young adults, that bed rest adds nothing to the regimen of chemotherapy alone. What I would like to ask Dr. Gibson is this: Does he think that there is any reason to believe that the antimicrobial drugs have indirectly made it possible to get patients up and around earlier by preventing recurrences, which otherwise would likely superimpose themselves on an infection which is already quiescent or perhaps still active?

DR. MAY G. WILSON, New York: I am old-fashioned enough to believe that until the cardiac reserve has returned to normal an increased load should not be placed on the dilated rheumatic heart. We have found, during short-term hormone therapy for an average of seven days, that the majority of patients feel fine in 24 hours and would be happy to be up and about. However, increase in cardiac reserve, regression of murmurs, and reversal of cardiac chamber enlargement was not observed until the 4th day of therapy. Only by the end of therapy, which was terminated abruptly, was the cardiac reserve normal. The children were on modified bed rest for one week after therapy was discontinued to observe for a rebound or a recurrence. They were discharged from the hospital within two to three weeks of the onset of therapy. They have retained their cardiac status as noted at the end of therapy for many months and years.

DR. MATTHEW L. GIBSON: Dr. Dorfman, regarding the selection of patients, actually we took the patients as they came to us and made no attempt to select anybody in whom we could positively, or at least as well as we were able to, diagnose acute rheumatic fever. As you well know, we were part of the joint study in most of this

* By invitation.

work still carried over from the extremely tight diagnostic criteria of that group, and we tried to be just as strict in the selection of this group. There was one slight variation from this. Last spring, several cases of chickenpox broke out in the ward. Because of reports of the severe spread of chickenpox to children on cortisone, we discontinued the cortisone therapy as rapidly as possible with the five children in the ward at that time who had not previously had chickenpox. Three of those five children had organic murmurs at the time they were discharged from the hospital. One of these has subsequently lost the murmur, so that two have cardiac murmurs today. In regard to Dr. Smith's question concerning any reason to believe antimicrobial drugs help in getting children up earlier by preventing the infection, I honestly cannot answer that. I do not know if it helps in getting children up early, but I know very well that no child that I treat for rheumatic fever is ever going to be without penicillin.

5. The Course of Acute Nephritis in Children Allowed Early Resumption of Normal Physical Activity. WALLACE W. MCCRORY, M.D.; DANIEL FLEISHER, M.D.,* and WILLIAM B. SOHN, M.D.,* Department of Pediatrics, University of Pennsylvania and The Children's Hospital, Philadelphia.

Rest in bed during the acute stage of nephritis (indicated by the presence of hypertension, edema, elevation of BUN, and macroscopic hematuria) seems empirically sound. The therapeutic value, however, of prolonged bed rest beyond the acute stage, in many instances until the urinary findings have returned to normal, has not been demonstrated to our knowledge. We wish to report observations on course and outcome of nephritis in 35 children who were allowed early ambulation after recovery from the acute stage. The patients included 9 girls and 26 boys whose ages ranged from 2 and 7/12 years to 12 and 10/12 years. Fifty-nine percent had hypertension during the acute stage of nephritis and fifty-seven percent had edema (decrease in body weight of greater than 10 percent after the acute stage). The longest period of complete bed rest during the acute stage was one month.

All subjects included in the study (initiated in 1953) were permitted to engage in normal physical activity, including attendance in school, two months after the onset of their nephritis. This program of early ambulation was instituted without regard to the activity of the renal disease as judged by laboratory signs (microscopic hematuria and elevation of erythrocyte sedimentation rate). Serial measurements of these laboratory signs were made, however, during convalescence until they became normal, and the findings will be discussed. Prophylactic administration of penicillin (300,000 units daily) was employed routinely with early ambulation and continued until the subject's Addis count had become normal.

One year after the onset of nephritis 29 of the 35 children were completely well (normal Addis count); 5 of the 6 not recovered by one year had a normal Addis count within two years after onset. We believe the recovery rate in these children (34 of 35) demonstrates the benign course expected for this disease in children. Early ambulation does not appear to have had an adverse effect on the ultimate course of their nephritis. We feel these observations lend no support to the widely held concept that physical activity per se is a major factor in predisposing a patient recovering from acute nephritis to reexacerbation or toward the evolution of chronic nephritis.

Discussion

DR. JAMES N. ETTLEDORF, Memphis: During the past three years we have conducted follow-up studies on 41 cases of acute nephritis in children. Our studies included serial Addis counts, routine urinalyses, renal clearances (endogenous creatine and urea clearances), and clinical check-ups. Analysis of our data has permitted us to arrive at the same conclusion as that reported by Dr. McCrory. Recently we have followed seven patients who were required to ambulate during the waking hours immediately after entering the hospital. Using similar criteria in evaluating this group we observed the same results as in those who were required to rest for the first month. It appears therefore that one month of bed rest is adequate unless unusual complications exist.

DR. MILTON RAPOPORT, Philadelphia: I would like to add some information that supplements what Dr. McCrory has presented. It is culled from a study that was published but was not designed to test the effect of ambulation. In 1942, we brought back 72 patients who had been in the Children's Hospital prior to 1935 with acute nephritis. Some of these came back 25 years after they had had their illness. None was brought back less than five years after the illness. All were evaluated by Addis counts, BUN studies, a cursory kind of urea clearance, complete physical examinations, and x-ray of the heart and EKG when indicated. These were compared with a group of 50 patients whom we had kept in the hospital until all the criteria which we were using as evidence of disappearance of nephritis were satisfactory. These were essentially the criteria that Dr. McCrory has presented to the group, sedimentation rate, Addis count, and routine urinalysis first, and then renal function tests. This was possible in the days when hospitals could afford to keep patients,

* By invitation.

and we probably were not too much concerned with the psychosomatic effects of hospitalizing children. Usually, there was no difference in the two groups. The first group had been discharged from the hospital in a casual sort of fashion. The first group returned to complete activity in almost all instances when discharged from the hospital on the average of about three and one-half weeks. No child had been hospitalized more than 30 days. The criterion for discharge was routine urinalysis done by a three- or four-year medical student, and the patients were discharged to return to the clinic periodically and go back to school or do whatever they wanted. There were no differences in the two groups. We had been interested in the development of chronic nephritis, which was what we were looking for. There was no chronic nephritis in the first group. Certainly, they had been casually ambulated at an early stage. We had always used this datum in teaching our medical students that it did not make much difference. This was a little different than passing it on to referring physicians, however.

DR. SOLOMON KAPLAN, Brooklyn: Fifteen years ago, I think, a paper appeared in *Lancet* entitled "On the Dangers of Going to Bed." I have forgotten the author. Now, Dr. McCrory might add a subtitle on the lack of danger of getting up. Acute nephritis has been known for many years as a benign disease. All attempts of the medical profession to make a severe disease out of it have really failed. We have, over the past four or five years in our own renal clinic, used early ambulation, and we have been impressed with the results in the promotion of well-being. I have one question for Dr. McCrory. I was surprised to see the A/G ratios. I think that Dr. McCrory gave the impression that the albumin was nearly always low in acute nephritis and the globulin was frequently high. In our laboratory, using as a protein precipitant 22.4% sodium sulfate, we very rarely find a reduction in albumin. As a matter of fact, we use this as a method of distinguishing those cases of acute nephritis which tend to overlap with the nephrotic syndrome.

DR. WALTER HEYMAN, Cleveland: For the last eight to ten years we have permitted children suffering from acute glomerulonephritis to be out of bed when hypertension and edema had subsided, their urinary findings had improved, azotemia decreased progressively, and they felt well. This was possible with most of them 5 to 10 days after admission to the hospital. At this time they were discharged and soon thereafter went to school, avoiding strenuous games and exercises, however. Unlimited activity was resumed after the sedimentation rate had returned to normal and the urine was free of protein and abnormal sediment. In accordance with Dr. McCrory's experience, our children did as well under this more liberal guidance than under the more rigid control of previous periods. Even though posture and activity have been shown to have some effect on proteinuria and urinary sediment, the ultimate outcome of acute glomerular nephritis in children does not seem to be affected by earlier and guided ambulation.

DR. FLOYD DENNY, Cleveland: Because of the possibility that there may be more than one etiological agent in acute nephritis and that the prognosis might depend on the etiology, I wonder if Dr. McCrory would tell us something about the etiology of the disease in his group of patients, particularly in the patient that developed chronic nephritis.

DR. SAMUEL KARELITZ, New York: In 1927, when I was working with Czerny, we studied a group of acute nephritics to determine whether gross hematuria disappeared more or less quickly in the ambulant patient as compared to those on bed rest. There seemed to be no appreciable difference. While those children had gross hematuria, they were not edematous nor did they have hypertension. I would also like to ask a question. How long is the penicillin prophylaxis continued? Judging by the slide, some changes occur for as long as two years. Would you continue penicillin for that length of time?

DR. JOHN JAMES, Dallas Texas: We have set up a study similar to that of Dr. McCrory, differing only in the fact that we are making use of control patients who are being kept in bed. The results in the first 20 of these patients, followed as long as 18 months, appear to confirm his findings that there are no adverse effects from early ambulation. We have an impression, but it is an impression only, because the numbers are small, that the urine remains abnormal for a rather longer time in those ambulated. Whether this is an effect of ambulation per se, or whether it is due to the increased risk of exacerbations from infections in those ambulated, as Dr. McCrory has suggested, we are not in a position to determine because we have not used prophylactic penicillin after discharge.

DR. RICHARD T. SMITH, Dallas, Texas: I would like to ask Dr. McCrory: What is the basis for penicillin prophylaxis in his patients? Acute poststreptococcal glomerulonephritis is at present most frequently the result of Type 12 infection, though, as pointed out by Dr. Denny, other types may be responsible. While it would appear desirable to allow a type-specific antibody response, treatment of the streptococcal carrier states required to prevent rheumatic fever may prevent this. However, since only one or few types of streptococci produce nephritis, it does not seem logical to employ continuous prophylaxis as recommended for rheumatic fever, which may be caused by any type.

DR. HENRY L. BARNETT, New York: I think it is interesting that most of us who are seeing large numbers of children with kidney disease agree with Dr. McCrory about early ambulation, as is apparent from the discussion here. However, we also are all spending a good deal of time with parents of children who have been kept in bed for six or eight months after an attack of acute nephritis. I am very glad to see this point raised at this meeting. I think one further point is of importance in this regard. At the very beginning of acute nephritis, I think one needs to begin to prepare the children and the parents for accepting the recovery of the child. The nature and reputation of nephritis is such that it is very easy for parents to consider the child sick for a very long time and be overconcerned about the child. I think that preparation for acceptance of recovery has to be given when one first sees the child. If the child can be ambulated, as Dr. McCrory suggested, and with which most of us agree, I think this acceptance is much better achieved.

DR. ALLAN M. BUTLER, Boston: I would like to accentuate by referring to three cases the nice emphasis that Dr. McCrory has placed on distinguishing care in the acute phase and later. One case reliably reported to me by a teaching hospital was that of a boy who, in the acute phase, on rising from bed and going to the toilet, was found dead of acute cardiac failure. The second, a boy of 8, whom I saw, had an acute coronary and hemiplegia during the first few days of acute hemorrhagic nephritis but fortunately recovered. The third case accentuated the other aspect which Dr. McCrory has presented. Two months ago, a 10-year-old boy came to me who had been diagnosed as having acute hemorrhagic nephritis at the age of 2. He had lived for eight years on restricted activity and had never been allowed to go to school. We found that this was a case of congenital hereditary hematuria, where there was absolutely no diminution of renal function. A renal biopsy specimen showed no evidence of chronic glomerular nephritis.

DR. WALLACE W. MCCRORY: This discussion has demonstrated to me the advisability of practitioners attending these meetings of the Pediatric Society rather than going to the library. As most of you know, our textbooks do not present the consensus regarding early ambulation that I have heard expressed here this morning. Dr. Kaplan, in answer to your question regarding the findings of reductions of serum albumin concentrations, we use a 27% sodium sulphate salt concentration for measurement of albumin. We regularly find some reduction in serum albumin concentration in these patients. We rarely find values below 2 gm. %. This is a reflection of spectrum of findings in such patients. Technical variations in methods make comparisons with findings of others difficult. It certainly has been our experience to find some reduction in serum albumin in the acute stage. In answer to the question regarding evidence of preceding infection, I have this information on a slide but unfortunately it is not here. Eighty per cent of these patients had histories of preceding upper respiratory infection. Our difficulty these days is that we get the patients one to two weeks after the acute illness. The majority come in after receiving penicillin or antibiotic therapy, so our rate of isolating β-hemolytic streptococci on throat culture is very low. Acute glomerular nephritis is diagnosed by a history of preinfection, urinary evidences of acute inflammation of the kidney, and the absence of evidence that other systems are involved. I would assume the etiology is the accepted etiology for glomerular nephritis. Prophylactic penicillin was stopped as soon as the patients' Addis counts were normal. The question of the basis of prophylaxis is, I think, important. If it is true that only a few strains of streptococcus are capable of causing nephritis, one would then anticipate that these patients have little likelihood of succumbing to reinfection to the same agent if they respond properly immunologically. Our reason for using prophylaxis was the feeling that the reexacerbations of nephritis do not require type-specific streptococci reinfection. We do not have data to prove this, but it has been our impression that reexacerbation could be provoked by an anamnestic response accompanying infection with any strain of streptococci. These patients generally will be found to have higher titers for antistreptococcal components than patients having streptococcal infection without nephritis. If you think of them as representing to a degree a hypersensitivity state, even though they are infected by types of streptococci other than those capable of causing nephritis, there could be a temporary reexacerbation of their nephritis. This, at least, was our premise.

6. Studies of Insensible Weight Loss, Clinical and Experimental.† GEORGE M. GUEST, M.D.; MARY D. PETTIT, R.N.*; CARLOS ARAUJO, M.D.*; JAMES FRID, M.D.*; BERNARD COMBES, M.D.*; C. DE MENIBUS, M.D.,* and EVA WITTGENSTEIN,* Department of Pediatrics, University of Cincinnati and Children's Hospital Research Foundation, Cincinnati.

Earlier investigators have reported much evidence that rates of insensible weight loss (IWL) could be closely correlated with basal metabolic rates determined by oxygen consumption or by calorimetry and, therefore, might constitute a valuable clinical

* By invitation.

† Partly supported by a grant from the U. S. Public Health Service No. A1531.

EXAMPLES, Clinical and Experimental Data

	IWL per Kg.	Gm/Hr. per Sq. M.
Human subjects		
Normal infant		
Male, 12 wk.	1.36	25.8
Normal adult		
Female, 26 yr.	0.62	22.3
Diabetic acidosis		
Female, 3 yr.,		
Kussmaul breathing	3.0	68.9
After recovery	0.9	39.8
Salicylism		
Male, 7yr.		
Rheumatic, receiving aspirin	2.01	53.9
Aspirin stopped	0.80	21.4
Hypothyroidism		
Cretin male, 10 wk.	0.71	14.1
Treated, Proloid 8 wk.	1.29	29.4
Hyperthyroidism		
Female, 5.5 yr.,		
Untreated	2.21	50.7
After treatment	0.83	20.2

Animals		IWL	Gm/Hr per Kg.
Dog, dinitrophenol 20 mg/kg.	Before		3.5
	After 1 hr.		19.4
	After 6 hr.		5.2
Cat, amphetamine	Before		1.5
	After 4 hr.		5.2
	After 12 hr.		1.0
Monkey, Serpasil	Before		2.0
	Asleep 9 hr.		0.8
	Asleep 12 hr.		0.5
Dog, "Hibernation" mixture of Phenergan, Thorazine, Demerol		Temp., F	
	Before	100	3.0
	Asleep 2 hr.	90	1.0
	Asleep 6 hr.	85	0.3

† Partly supported by a grant from the U.S. Public Health Service No. A1531.

diagnostic aid in studies of hypo- and hyperthyroidism. The earlier studies were made with delicate beam balances capable of measurement of small weight losses over short periods of time, but only with subjects at complete rest and mostly with normal subjects. For the studies to be reported here, an apparatus for continuous recording of weight was developed, which permits measurements of IWL in nonresting as well as resting subjects. Standard Toledo scales are employed, one with 25 kg. capacity, for infants and small animals, the other with 135 kg. capacity. Weight is recorded electrically on paper pulled by a kymograph past the indicator needle of the scale and other fixed needles adjusted to trace calibration lines. The indicator needle, swinging with respiratory and other movements of the subject, makes a tracing that drifts across the paper with loss of weight. A line drawn through the tracing, extrapolated to cross the calibration lines, permits close estimation of weight loss in automatically measured intervals of time. The loss is then expressed as grams per hour per kilogram of body weight and/or per square meter of body surface. The apparatus was initially developed for studies of IWL in conditions associated with severe hyperventilation (e. g., in diabetic acidosis and salicylate poisoning) when restlessness and movements of labored breathing preclude the use of more delicate balances. The procedure has been applied in studies of the effects of respiratory-stimulant and depressant drugs, metabolic stimulant and depressant drugs, for studies of the effects of therapy in cretin infants and in young children with hyperthyroidism. Examples of data collected in these studies will be presented.

Discussion

DR. SYDNEY SEGAL, Vancouver, B. C.: I would like to report yet another application of Dr. Guest's method, which was sparked by a visit to the laboratory of Dr. James Sutherland in Cincinnati and by a report published some years ago by Drs. Clement Smith, Donagh O'Brien, and John Hansen. In formulating a program for some student research, we were able to put students onto the problem of extending Dr. Smith's work in order to show the actual insensible losses at various relative room humidities and in supersaturated atmospheres. The problem given to the students was to determine the exact relationship between insensible weight loss and the various degrees of relative humidity. They were given no expense money for equipment, but worked out something useful, though not nearly as elegant an apparatus as Dr. Guest has shown. You will see that this is an incubator. The baby is suspended from an ordinary baby balance, and the beam of the balance has been extended with a piece of erector set which goes to the kymograph record. The baby lies in a sling made of nylon mesh and in the incubator which has the advantage of constant recirculation of the contained air. The relative humidity is read on a meter seen on the left. The recordings are similar to those reported by Dr. Guest. This is an application of the IWL method for the study of body water economy, and I would like to have Dr. Guest's comments, if he will give them, on this kind of application, as distinct from the study of metabolic rates discussed so far.

DR. WALLACE W. MCCRORY: On one slide describing salicylate poisoning, if I read the figures

correctly, you found water losses of 1.5 gm. per kilogram per hour. If I am incorrect, simply state so. If I am correct, I would appreciate a comment since this seems to be in the range of normal rates of water loss. One assumes there is usually a marked lung water loss in such states. Would this mean there was a decrease in skin loss?

DR. RALPH WEDGWOOD, Cleveland: One of our medical students has used this machine most effectively to measure spontaneous activity rates in infants. She has done this by counting the number and the amplitude of the jiggles over various periods of rest and activity.

DR. GEORGE M. GUEST: I am glad indeed to see the photographs showing another successful approach to the problem of continuous recording of weight of infants. We, too, did a great deal of "gadgeteering" in various attempts to solve this problem, using several different types of balances, kymographs, writing levers, and smoked paper for continuous recording of weight before we adopted the apparatus described here. Without attempting to review earlier investigations, I should like to mention the studies by Benedict and by Lombard, each of whom used writing levers and smoked paper for continuous recording of weight and movements of adult subjects resting on delicate beam balances, some thirty and more years ago. It is indeed feasible to obtain good results along these lines with a variety of scales and recording apparatus. Replying to Dr. McCrory, I should note that the rate of insensible weight loss for the one example of salicylate poisoning shown here was not much above the average normal. The tracing shown was selected primarily to show the pattern of violent respiratory movements of hyperventilation and to demonstrate the practicability of this method of recording, despite the movements of the infant. In the case represented by this tracing the infant was severely dehydrated. With very dry mucous membranes of the respiratory tract after prolonged hyperventilation it seems likely that the loss of water vapor may be slower than in earlier stages before such severe dehydration has developed. In other examples of salicylate poisoning in infants the observed rate of insensible weight loss has been as high as 5 gm. per kilogram per hour. Dr. Wedgwood's report of the use of the scale for recording and measuring activity rates of infants merits emphasis. For this purpose the kymograph can be operated at different speeds to pull the recording paper faster than the usual speed of 1 in. per 5 minutes; e. g., 1 in. per minute, 4 in. per minute, or faster. At higher paper speeds one can clearly discern changing patterns of respirations, periods of apnea, muscular twitching, slight convulsions, hiccups, etc. Thus the apparatus can serve as a valuable tool for studies of respiratory physiology.

7. Disturbances of Acid-Base Equilibrium in Salicylate Intoxication. ROBERT W. WINTERS, M.D.,* and NELSON K. ORDWAY, M.D., Department of Pediatrics, University of North Carolina School of Medicine, Chapel Hill, N. C.

The disturbances in acid-base equilibrium occurring in 33 cases of salicylism in infants and children have been studied. In all patients, the plasma total CO_2 content and the calculated CO_2 tension (pCO_2) were reduced; whole blood pH was low in some patients, normal in others, and elevated in still others. A comparison of the initial acid-base data on the acidotic subjects with similar data on 61 infants and children with metabolic acidosis due to diarrhea reveals that the patients with uncomplicated salicylism had lower values for pCO_2 at any given blood pH than did those with diarrheal acidosis. This finding suggests that the basic acid-base alteration in salicylism with acidosis is a mixed one with primary independent coexistent disturbances in the metabolic component on the one hand and in the respiratory component on the other. Salicylism with acidosis differs from metabolic acidosis due to other causes, in which the disturbance in the metabolic component is the primary event while the change in the respiratory component is secondary and compensatory.

The existence of a mixed disturbance was identified in some of the patients presenting with normal or alkaline blood pH values by the finding of a significant increase in the R fraction of the serum (calculated as serum Na−[serum Cl+serum CO_2+serum salicylate]) associated with profuse ketonuria. The remaining patients with normal or alkaline values for blood pH had no elevation of undetermined anion and no ketonuria; presumably such patients represent respiratory alkalosis with secondary metabolic compensation of variable degree.

The nature of the metabolic disturbance was investigated by the study of the anion partition of the serum of five patients with acidosis. Elevations of serum chloride and undetermined anion (the last calculated by difference as [Na+K+Ca+Mg] −[HCO_3+Cl+phosphate + salicylate + protein]) were uniformly present, hyperphosphatemia was present in only one instance.

These studies emphasize the complexity of the disturbances of acid-base equilibrium occurring in salicylism. Respiratory stimulation is a uniform finding in nearly all patients and is presumably due to a direct stimulatory effect of the drug on the respiratory center. When this is the only effect, respiratory alkalosis results. In the majority of

* By invitation.

circumstances in children, salicylate may cause an additional disturbance leading to ketosis. When this is superimposed upon respiratory stimulation, a mixed disturbance results. In this view, the final effect upon blood pH will be governed by the largely fortuitous balance occurring between the intensity of respiratory stimulation on the one hand and the intensity of the metabolic disturbance on the other.

Discussion

Dr. Samuel Bessman, Baltimore: I would like to cite some experimental work that was done while I was an intern in support of this delicate demonstration of the disassociation of the respiratory alkalosis from the metabolic acidosis. In the first place, when a patient has salicylate intoxication, the serum pyruvate level is elevated, indicating a lesion at the level of oxidation of pyruvate. This can further be borne out by experiments with liver slices in which liver respiration is inhibited by levels of salicylate equivalent to the toxic levels found in the blood. Furthermore, liver slices which have been poisoned with salicylate do not produce ketoglutarate, but they will produce it when citrate is added. In other words, there is a lesion at the level of the Krebs cycle. This peculiar type of respiratory effect is also seen in ammonia poisoning, in which again you get hyperventilation. The hyperventilation alkalosis again is due to a lesion of the Krebs cycle.

Dr. Solomon A. Kaplan, Brooklyn: I would like to cite some new evidence which pinpoints the disturbance of metabolism in salicylate poisoning. This paper, although published in 1954, seems to have escaped the attention it ought to have received. Experiments were described in which homogenates of liver were incubated with various substrates and salicylate. It was found, in contradistinction to what Dr. Bessman has just said, that in the presence of salicylate homogenates of liver were unable to oxidize ketoglutarate and succinate. The experiment is very interesting, because the first step is magnesium-dependent. The inhibition could be overcome in this step by adding excess magnesium ions. It is known that salicylates are chelators. The possibility arises that salicylates are actually chelating magnesium, and thus interfering with conversion of α-ketoglutarate to succinate. This sets up a nice hypothesis for explaining the finding of ketone bodies in salicylate poisoning. The hypothesis is similar to that used for diabetic acidosis. The Krebs cycle is no longer turning, so that the four-carbon residues of fatty acid oxidations pile up in the blood stream. I want to ask a question about the relationship between the alkaline pH and the ages of the children. It has been my experience over several years in which we have diligently looked for this that it is very rare to find respiratory alkalosis in an infant under *2* years of age. In older children who have received large doses of salicylates, this is not uncommon. This is an important point because it bears on the whole question of bicarbonate administration.

Dr. Henry L. Barnett, New York: I would like to ask what the relationship was between the pH of the plasma and the pH of the urine, particularly in those children who had an elevated serum pH.

Dr. Samuel Spector, Cleveland: I should like to ask the authors whether they noted any correlation in their patients between the duration of salicylate intoxication and the presence of either respiratory alkalosis or metabolic acidosis? Somehow in the literature the statement reappears that if more than six hours has elapsed since the time of salicylate ingestion, the child will usually present with metabolic acidosis. In our experience, although a rough correlation does exist between the elapsed time of intoxication and the development of acidosis, it has been unpredictable. This question of predictability of the acidosis becomes more important since the recent reemphasis of the use of bicarbonate in this type of patient to produce an increase in urinary excretion of salicylate. Also, and in answer to Dr. Barnett, we have found little correlation between urinary and blood pH. It would seem to us necessary to know the blood pH before administration of bicarbonate, as the blood pH appears to us the only way one can be certain of the status of the acid-base equilibrium.

Dr. George M. Guest, Cincinnati: This was an excellent analysis of the several complicated factors in the mixed picture of metabolic and respiratory disturbances that characterize salicylate intoxication. It may be useful to emphasize the sequence of events in the development of salicylate intoxication in the order of their development, as well as the relative importance of separate factors in the metabolic derangements observed during successive stages. Variation in individual susceptibility to salicylate may be an important factor influencing the course. The first stage is characterized by respiratory alkalosis, resulting from hyperventilation provoked by the effects of salicylate on the respiratory center of the brain, with lowered serum CO_2 tension and elevated serum pH but with little change in the pattern of serum electrolytes, bicarbonate, sodium, and chloride. The second stage may be described as one of "compensated" respiratory alkalosis, with normal serum pH, lowered serum bicarbonate, and the changing pattern of other electrolytes well described by Dr. Winters. Several more or less separate physiologic mechanisms play variable roles with the changing conditions. In some instances, the lowered serum bicarbonate is matched mainly by lowered concentration of sodium, in others, mainly by an elevated

concentration of chloride. In a third stage, the development of metabolic acidosis is superimposed upon the antecedent state of respiratory alkalosis. Here the important factors are dehydration, hemoconcentration, and secondary effects of impaired renal function that follow dehydration. The development of ketonemic acidosis at this stage can be ascribed to liver damage and starvation, especially in the presence of vomiting. Recognition of this sequence may clarify the confusion that sometimes arises in discussions of respiratory alkalosis and/or metabolic acidosis of salicylism when the changing pictures and separate concepts seem paradoxical.

DR. THOMAS K. OLIVER JR., Columbus, Ohio: Dr. Winters indicated that lactate rises in any state of prolonged respiratory alkalosis and suggested the possibility that chloride may do this same thing. It is well known that respiratory alkalosis from any cause will cause significant chloride shift from red cells. What role does the respiratory alkalosis alone play in the subsequent development of metabolic acidosis? Secondly, I wonder if he has any information bearing on the point of the duration of the effect, following a single challenge of salicylate, of stimulation of the respiratory center. There is some question as to whether this is short-lived or may last for as long as 24 or 48 hours.

DR. WILLIAM E. SEGAR, Indianapolis: In connection with the comments of Dr. Bessman and Dr. Kaplan about the effect of aspirin on carbonate metabolism, I would like to report that we have five or six patients with severe aspirin poisoning, who have been hyperglycemic and have had high blood sugar levels for 7 to 10 days after intoxication with salicylate. I wanted to ask Dr. Winters if he has any comparable experience.

DR. ROBERT W. WINTERS: I can add very little to the discussion of intermediary metabolism. It seems to me that it is in this area that we must look to explain the mechanism of the ketosis which develops in these children. Dr. Kaplan's impression of ketosis occurring in young children but not in older children and adults is comparable to ours. Dr. Barnett asked about the pH of the urine. The urines are uniformly acid in spite of systemic respiratory alkalosis. We have not encountered any urines which would be called frankly alkaline. I think that all of these patients have paradoxical aciduria if they have salicylism of any serious degree. I would certainly agree with the comment that was made that one cannot infer the blood pH from the urine pH under these circumstances. With respect to the correlation of duration and the type of acid-base disturbance which one encounters, we have done this for all of the data in the literature. There is a great deal of spread and no consistent pattern, save the fact that when the duration is longer than 24 hours, the blood pH is always acid. However, durations of longer than 24 hours occur exclusively in children who are already ill and who have become intoxicated with salicylates in a therapeutic situation. Whether or not it is duration or the nature of the situation in which the child becomes intoxicated, I do not know. Both will correlate. Dr. Guest has reviewed several very important points. I would only like to add that the development of potassium depletion is frequent in our experience in this particular disorder. Dr. Oliver asked about "excess" chloride. It is true that one could interpret the data to indicate that "excess" chloride might represent the compensation by the kidney to a preexisting respiratory alkalosis. On the other hand, we have seen elevations of chloride occurring in children in whom the duration of salicylate poisoning was very short. In looking over a very recent paper in the *American Journal of Physiology* by Dr. Brodsky, I noted that when he infused β-hydroxybutyric acid, chloride excretion fell. This would imply that the reabsorbate would have a larger amount of chloride in relation to the sodium. It may be that the mechanism that he has suggested in that paper is operative in salicylism. What is the duration of the respiratory effect of a single dose of salicylate? I do not know that. The change in the sensitivity of the respiratory center to pCO_2 and hydrogen ion is in dispute. Dr. Alexander has shown that an increase in sensitivity occurs within an hour or so after a dose of aspirin was given. On the other hand, Dr. Tenney did not find a change in sensitivity until 24 hours. I have no answer to Dr. Segar's question. We have not found hyperglycemia in excess of 170 mg. % in our patients. One can easily produce hyperglycemia experimentally by giving an animal salicylate and an adrenal steroid. Under these circumstances, there is a significant increase in blood sugar, considerably more than with either agent alone.

8. Experimental Water Intoxication. JOHN D. CRAWFORD, M.D.; PHILIP R. DODGE, M.D.,* and JAN H. PROBST, M.D.,* Departments of Pediatrics and Neurology, Harvard Medical School, and the Children's Medical and Neurological Services, Massachusetts General Hospital, Boston.

Water intoxication is recognized with increasing frequency but many aspects of its pathogenesis and therapy remain obscure. This has stimulated experimental reproduction of the syndrome in anesthetized (barbiturate or curare) or unanesthetized rabbits during which the following observations have been made.

Water intoxication can be induced at a controlled rate by intravenous infusion of 2.5% dextrose and

* By invitation.

water containing 0.2 mU. per milliliter of vasopressin, the effect of the hormone being merely to reduce the amount of infusate necessary. Electroencephalographically, induction is accompanied by a gradual disappearance of the high frequency activity, reduction in the amount of 4 to 7 per second activity, and the emergence of 1 to 3 per second activity. In the late stages discharges of all frequencies rapidly diminish in voltage. These changes are accompanied by a marked rise in cerebrospinal fluid pressure. However, they cannot be reproduced during infusion of isotonic saline by a similar rise in cerebrospinal fluid pressure resulting from elevation of a communicating fluid filled external reservoir. They cannot be prevented during infusion of hypotonic fluid when pressure is maintained normal, using the external reservoir as a damp. Venous pressure also rises during induction but this change does not affect the electroencephalogram. The brain itself becomes grossly edematous and shows reduction in both sodium and chloride content with gain in water per unit of dry defatted solid.

Serum concentrations of total solute, sodium, chloride, and potassium fall during induction of intoxication in inverse proportion to the rate of water accumulation in the body. Plasma, extracellular, and intracellular fluid volumes are expanded. Potassium losses from either body or brain intracellular fluid are negligible.

Reversal of the abnormal electroencephalographic pattern, reduction in spinal fluid pressure, elevation in serum osmolality, and diminution in the volume of the total body intracellular compartment, irrespective of the changes in extracellular or plasma volumes, all occur rapidly when the hypotonic infusion is replaced by hypertonic saline (3%) or mannitol (15%). When the latter fluid is infused, serum sodium and chloride values continue to decline.

These observations suggest that hypotonicity and intracellular edema of the brain are important determinants of the neurological disturbance in water intoxication, that the electroencephalogram may be useful in diagnosis and in guiding therapy, and that neither hyponatremia nor hypochloremia are prime determinants of the syndrome. Mechanical relief of increased intracranial pressure would seem to have no place in therapy, but hypertonic mannitol may be considered as an alternative to hypertonic saline.

Dr. Laurence Finberg, Baltimore: I would like to express appreciation of these studies and point out that if the opposite insult is given to an animal, with infusion of hypertonic solution, there are also changes in the nervous system and in the spinal fluid pressure in the opposite direction. I think that this is quite obvious. The only importance is that when one is going to use hypertonic solutions to correct, one wants to make sure one does not overcorrect and cause trouble in the other direction. I would also like to ask Dr. Crawford what the results of the tissue analysis were. He may know whether electrolyte shifts and ionic adjustments, caused by association with the cell, the reverse of what we see in hypernatremia, also occurs in water intoxication.

Dr. William A. Brodsky, Louisville: I would like to ask if the interpretation of a normal or an increased source of electrolytes takes into account that there might be a large shift of water and electrolytes into the lumen of the gastrointestinal tract? If so, was there any attempt to measure spaces?

Dr. Daniel C. Darrow, Mission, Kan.: Can you tell us a little bit about the analysis of the brain?

Dr. John D. Crawford: I anticipated questions about brain chemistry. Unfortunately, one cannot make serial determinations on the same animal. At present, we are limited to analyses of brain in our animals before the start of water intoxication and at the height of its development. We have not yet accumulated significant data with regard to brain composition following treatment. What we find is that the tissue water at the height of intoxication is increased by 16% per 100 gm. of dry defatted weight. In these animals, the mean expansion of the extracellular compartment calculated on the basis of the chloride assumption is 28%; the mean expansion of the intracellular space is 9%. It seems from our limited analysis that electrolytes are lost from the brain tissue during this process of hypotonic infusion. The losses in the data thus far average 19% for chloride and for sodium. There is little, or no, significant loss of potassium. Tissue sodium at the concentration of plasma ultrafiltrate is just adequate to fill the extracellular space. There is none left over for intracellular position either in the normal animals or the animals at the height of intoxication. In brief answer to Dr. Brodsky's question, we have not made any attempt to follow shifts of electrolytes into or out of the gastrointestinal tract.

9. Effects of Acute Changes in Extracellular Fluid Composition on Bone Sodium Content.

Gilbert B. Forbes, M.D., and Richard B. Tobin, M.D.,* Departments of Pediatrics and Physiology, University of Rochester, Rochester, N. Y.

The fact that skeletal tissues are rich in sodium, together with the observation that a portion rapidly exchanges with radiosodium, has attracted the attention of a number of investigators. Studies have been reported on the net change in bone sodium content produced by various experimental situations. Bergstrom, Levitt, Nichols, Woodbury, and their coworkers have concluded that acidosis and/or salt depletion are the principal stimuli responsible

* By invitation.

for affecting a net decrease in bone sodium content. Investigations of synthetic hydroxyapatite systems have led Neuman to conclude that the sodium content of bone is a reflection of the extracellular fluid concentration of this ion, and that sodium exchanges for calcium on a mol for mol basis on the crystal surface.

Acute changes in extracellular fluid composition were induced in cats by the infusion of a variety of solutions, including HCl, NH_4Cl acetic and lactic acids, NaOH, $NaHCO_3$, NH_4OH, hypertonic NaCl, and glucose-water. These solutions were infused at a maximal rate over a two hour period, and the bone sodium content in these animals compared to that of a control group. Radiosodium was given to some animals to determine exchangeability. In all, 88 animals were employed in the study.

Except for HCl, all of the treatment produced a significant decrease in bone sodium content, in the amount of 4 to 8%. Contrary to expectation, alkalosis was accompanied by as much of a fall in bone sodium as acidosis, and hypernatremia by as much as hyponatremia. No correlation could be found between changes in blood pH, serum Na, serum bicarbonate, or serum Ca levels and the fall in bone sodium, nor was there a correlation with water load, acid load, or change in total extracellular fluid sodium content. Sodium loading did not bring about an increase in bone sodium. The maximum fall amounted to about one quarter of the rapidly exchangeable fraction as measured by radiosodium exchange.

It is apparent that a variety of alterations in extracellular fluid composition can bring about a modest decrease in bone sodium content and that acidosis and hyponatremia are no more effective than a number of other factors. The question of whether bone, as regards sodium content, is truly responsive to a variety of influences or whether the treatments used all involve a common denominator is a subject of continuing study.

Discussion

Dr. Daniel C. Darrow, Mission, Kan.: I have been interested in bone sodium ever since Dr. Harrison showed the relationship of it to bone calcium. If we think of the chemistry of it, we should not expect these exchanges necessarily to be related to changes in pH. As I understand it, it is present as a carbonate, and it has to have the hydrogen ion acting with the carbonate in order to free the sodium as sodium bicarbonate. The reaction requires an anion to neutralize the positive charge of Ca on the bone salts. The anion is not HCO_3 since bone CO_3 decreases in acidosis. I was especially interested in your demonstration here, which is completely unrelated to the pH as far as I can see. I am wondering whether it is not related to the metabolism of some such acids as citric acid which, reacting with a surface layer on the crystals, can exchange in that sort of fashion.

Dr. Donald Gribetz, New York: In our laboratory, we have utilized two more "chronic" stimuli in an attempt to test a similar situation, i. e., whether bone releases its sodium in response to slower changes in extracellular sodium concentration. We have employed the edema of rat "nephrosis" and the edema resulting from DOCA administration in the same animal. We must agree with you in that our data showed no significant shifts of sodium from bone into the extracellular fluid, at least in response to these two stimuli.

Dr. William H. Bergstrom, Syracuse, N. Y.: I should like to comment on the magnitude of the project which Dr. Forbes has presented. The task of doing so many of these tedious analyses in animals is little short of monumental. The composition of bone does not vary between one mammalian species and another. The accessibility of sodium, however, probably relates less to the chemical composition of the bone than to the actual physical distribution of fluid and solid within the bone itself. There is a difference in this respect between animals of different ages and species. In other words, either gross or microscopic morphological differences may account for the changes in accessibility of this ion. It is therefore evident that results obtained in one species may not necessarily be reproducible in another.

Dr. Gilbert B. Forbes: I do not believe there were any direct questions asked of me except by Dr. Darrow in speculating about the mechanisms involved. I believe that in my introduction to this presentation I gave you the only concrete speculations that have been made to date. I think we can safely say that the exact nature of the factors responsible for the existence of sodium in bone and for its net exchange, even though this may be small, are not understood.

10. Hyperkalemic Periodic Paralysis. Thomas Egan, M.D., and R. Klein, M.D., Department of Pediatrics, University of Pittsburgh School of Medicine, and the Children's Hospital of Pittsburgh.

We have studied three members of two separate families who suffer from the hyperkalemic variant of familial periodic paralysis. Paralytic episodes always occur at rest and are more severe if the rest period is preceded by a period of exercise. Fasting and cold predispose to attacks. Ingestion of the potassium in cantaloupe produced severe attacks in some patients. The trait was transmitted as an autosomal dominant. However, one boy's father and grandfather had not had the attacks, though his great-grandfather had. Blood and urine specimens were obtained from three patients before,

* By invitation.

during, and after an attack. Arterial blood was obtained from an arterial catheter on one occasion. Otherwise arterialized capillary blood was used. The venous and arterial bloods were obtained from the same arm nearly simultaneously. The subjects and controls were given glucagon and epinephrine and their responses to these agents were studied.

Venous pH, CO_2 content, calcium, and magnesium did not show any significant change. Urine bicarbonate excretion increased during the recovery period and urine pH was raised. Creatinine excretion did not change. Urine and serum corticoids did not differ in patients and controls. They were high but unchanged during attacks. Serum proteins and whole blood hematocrit did not change in these studies. ECG changes reflected serum K.

Our patients showed a rise in serum potassium preceding and during the attack, sometimes with increased peripheral uptake of potassium. Serum sodium rose during the attacks, falling in the remocery period, as did the potassium. Serum and urinary phosphorus changes in the patients were similar to those in the controls. There was no evidence of any interference with glucose metabolism.

Our studies indicate that the rise in serum potassium may be associated with an increased rather than a decreased forearm uptake of potassium. A rise and fall in arterial potassium may be produced by shifts of potassium in or out of viscera, red blood cells, or other more severely affected muscles. Decreases in arterial potassium values also occurred in the normal controls following glucagon and epinephrine without evidence of increased peripheral uptake. Similar falls in phosphorus concentrations occurred in both the patients and the controls. In the recovery period there was no increase in uptake of potassium in the forearm of our patients. Elevation of the blood sugar of two patients, produced in one case by glucagon and in the other by glucose ingestion, led to no increases in peripheral uptake of potassium, but to a release of potassium from the forearm to the venous circulation. This might help explain the pathogenesis of the attacks. This inhibition of peripheral uptake of potassium would lead to a low muscle potassium, and a slight increase in extracellular potassium concentration could be expected to produce paralytic effects in our patients but not in normal individuals.

We have demonstrated an increase in excretion of a sodium-losing hormone in the urine of one pregnant patient so studied. This was of modest degree. If this finding can be confirmed, it is consistent with the theories to be advanced and helps to explain the pathogenesis of the syndrome.

Discussion

DR. HAROLD E. HARRISON, Baltimore: I would be very curious about the source of that extra sodium. Where does that sodium come from? It has been implied that it does not come from muscle. If it did not come from muscle, one would have to speculate on an abnormal composition of muscle. What tissue could be responsible for the source of marked increase in sodium? I wonder if any attempts have been made to analyze tissues and red cells or whether exchangeable sodium has been determined in these patients to indicate if there is some marked abnormality of tissue composition with respect to sodium and potassium ratios. It is a rather bizarre finding.

DR. THOMAS EGAN: Dr. Harrison, in our postulations we had to presume that in the one instance where we could not account for the sodium deriving from peripheral tissues, it must have been drawn from elsewhere in the body. Observed attacks of paralysis in the same subject on different occasions have shown no symmetry of the paresis. One arm can be involved to a greater extent than other extremities, and it is possible that measurements in this one instance in which we could not account for the sodium rise peripherally have been taken on an arm which was affected to a lesser extent than other areas of the body. We have not performed studies on the tissues of our patients and this would be a logical step. We have studied the red blood cells as a factor in producing the observed changes, but our studies do not suggest this possibility.

11. The Syndrome of Infantile Nephrosis. HOWARD G. WORTHEN, M.D.*; ROBERT L. VERNIER, M.D.,* and ROBERT A. GOOD, M.D., The Pediatric Research Laboratories of the Variety Club Heart Hospital, University of Minnesota, Minneapolis.

Infantile nephrosis is a characteristic syndrome which is differentiated from the nephrotic syndrome of older children by an almost universal failure to respond to therapy and by an extremely poor prognosis. We have studied 12 patients with this syndrome. Six patients became edematous within the first few days of life and undoubtedly had proteinuria at or before birth. In one instance, marked proteinuria was demonstrated in the first urine specimen. The remaining patients developed frank clinical nephrosis between 3 to 11 months after birth. In all patients, the physical and laboratory findings were characteristic of the nephrotic syndrome. Various forms of therapy were tried, including ACTH, cortisone, nitrogen mustard, malaria, and albumin. The kidneys of all were examined histologically, by renal biopsy and/or autopsy.

* By invitation.

The nephrosis in one patient seemed definitely related to mercury intoxication. This patient had an excellent response to ACTH therapy, and is well at present. None of the other patients have responded to treatment, and at present, eight are dead and three have active disease.

Although infantile nephrosis is a characteristic syndrome, it is not a disease entity since at least two forms can be distinguished by a dissimilar pathologic picture. In one, the picture is dominated by tremendous tubular dilatation and distention of Bowman's capsule. In the other, the changes resemble those of older nephrotics, varying from thickened basement membranes to severe chronic glomerulonephritis. Although the microscopic changes observed in the kidneys of some of these children are identical to those described by Giles et al. in 1958, we have been unable to demonstrate the accumulation of crystalline material in the liver, spleen, and kidneys that was described by these authors. Electron microscopic studies of ultrathin sections reveal that in both forms of infantile nephrosis the characteristic basement membrane changes, observed in children with other forms of nephrosis, were present. This observation suggests that, although striking tubular abnormalities may be observed in infantile nephrosis, the lesion responsible for the nephrotic syndrome, as in other forms of nephrosis, is probably located in the glomerulus.

The autoantibody theory concerning the pathogenesis of nephrosis seems less tenable in this group of children than in older nephrotics, since the disease in these cases develops and progresses during the neonatal immunologic null period.

Discussion

DR. HENRY L. BARNETT, New York: I would like to ask two questions. One is whether complement was measured in these children. The second is whether the authors have seen additional cases of nephrosis associated with mercury ingestion. The typical picture of nephrosis has been described with gold therapy by the French. Mercury, obviously, can cause acute renal failure or acute tubular nephrosis. I do not know of reports in the literature in which mercury has caused the typical picture of nephrosis, as described in one of the patients presented here.

DR. WALTER HEYMANN, Cleveland: Among 218 cases of nephrosis that we have had in Babies and Children's Hospital in Cleveland during the last 20 years, the youngest one was a baby 6 months of age, who did well. One newborn baby that was in the pediatric service at Cuyahoga County Hospital was reported by Dr. Eiben: that baby died of aspiration pneumonia after ACTH induced diuresis. To have 12 cases in a period of six years is astonishing and points to an important difference of the material seen in these two regions. Even if we deduct the five familial cases and the one that possibly may be due to mercury, there are still six cases of nephrosis in young infants left, which is an unusually high incidence. I would like to ask Dr. Worthen how large the total nephrotic population was from which the 12 infantile cases were derived. I have one further comment, which refers to the electron microscopic studies that the authors presented. Two or three weeks ago, the Association of American Pathologists met in Cleveland. One of the pathologists reported on electron microscopic studies of kidneys of newborn infants. They seem to be different. The epithelial podocyte layer of the glomerular basement membrane is not as well differentiated as in the older age groups. The findings of Dr. Worthen thus would have to be controlled by electron microscopic studies of infants of equal ages. If it is true that the podocyte layer of the newborn kidney is different, and if the nephrotic disease process is chiefly affecting that layer, this could provide an explanation for the different course of the disease in that age group, even if the etiology was not different. However, the accumulation of 12 cases in one region, not seen in similar frequency in another, would suggest another etiologic mechanism as well.

DR. MARC F. HANSEN, Madison, Wisc.: We have seen three such patients in the last year. The most recent of these fits into the second group of six patients and presented after about 3 months of age. The baby has subsequently responded somewhat to therapy and is in remission at the present time. However, the other two babies were essentially identical to the first three patients presented and were siblings. Our findings were in all respects th same as yours, but we had one further finding which I would like to ask a question about. The tissues from these two babies, two kidney samples, showed very marked arteriolar changes. In one infant, the biopsy was at 14 days, and the specimen showed marked changes of arteriolar nephrosclerosis, even though at that time there were no observable changes of the glomerular structure by light microscopy. I would like to ask if you have observed that on your sections.

DR. CONSTANTINE ANAST, Columbia, Mo.: In the last six months, we have seen two infants with nephrosis, one with onset in the first 3 days of life; the other with onset at 3 months of age. These are from two unrelated families. Each of these infants had older siblings who died of the same disease. The infant whom we followed from the first week of life and who is now 5 months of age has had a persistently elevated serum phosphorus, in the region of 10 mg. %, with a low phosphorus clearance. I wonder if you would comment on this.

DR. CHARLES B. REINER, Brooklyn: The cases portrayed with the pronounced dilatation of tubules present a picture that I think is probably consistent with polycystic disease of the kidney, which can produce a nephrotic syndrome in the newborn period. The cysts are often associated with lesions of the liver, pancreas, and occasionally lungs. I wonder if the authors observed such lesions in their cases, if any came to autopsy.

DR. D. H. BOWDEN, St. Louis: I recently saw my first case of infantile nephrosis. The glomerular changes were typical, but the pronounced tubular dilatation resembled a congenital defect and suggested that the renal injury may have occurred in utero.

DR. SAMUEL J. FOMON, Iowa City: Wedged between the states of Minnesota, Wisconsin, and Missouri, is Iowa, and we have not seen any.

DR. HARRIET G. GUILD, Baltimore: We have had two patients with this syndrome within the past seven years. The first patient was a baby who came to us at the age of 5 weeks. Apparently normal at birth, with a weight of 8 lb., she started vomiting almost immediately and had continued to vomit frequently, presenting feeding difficulties and a recurring anemia, in spite of transfusions, with eventual appearance of edema. Retrograde pyelograms done elsewhere before admission, because of albuminuria and nitrogen retention, revealed no gross anatomical abnormality of the kidneys. The nonprotein nitrogen mounted steadily, edema increased, and convulsions supervened. Admitted at this stage with a nonprotein nitrogen of 176 mg. %, acidosis, and a marked electrolyte distortion, the baby died within a few days. Laboratory findings were typical of the nephrotic syndrome except for the fact that the serum cholesterol was low (only 180 mg. %). At autopsy the kidneys were large and pale with marked fetal lobulation. On cross section, there was no distortion of the gross architecture. On microscopic examination, however, there was marked cystic dilatation of the tubules with atrophic epithelium and with hyaline casts occupying the lumen. By contrast, the glomeruli were extremely small and imperfectly developed. The second patient, admitted at the age of 4½ months, was said to have been well until 5 weeks before admission, when an upper respiratory infection with diarrhea was followed by vomiting, which had continued to occur several times a day from there on. On the day before admission periorbital edema was noted, and within 24 hours edema became generalized. The kidneys were palpably enlarged, albuminuria was marked (4+), and occasional casts and red blood cells were noted in the sediment. Again, laboratory findings were typical of the nephrotic syndrome with hypoproteinemia, an elevated cholesterol level of 316 mg. % which rose rapidly to a high of 920 mg. %, and a characteristic electrophoretic pattern. Resistant to therapy, the baby succumbed to an intractable diarrhea, with steadily rising nonprotein nitrogen from a level of 47 mg. % on admission to a terminal 156 mg. %. At autopsy, the kidneys were large and pale, again without distortion of the gross architecture. And again, on microscopic examination, there was marked dilatation of the tubules out of all proportion to what is seen in an ordinary nephrosis, although not as extreme as in the first patient. The epithelium was atrophic and the tubules contained "hard"-appearing hyaline casts. The glomeruli showed hypercellularity characteristic of a focal glomerulonephritis. It has been suggested by the pathologists that these kidneys may represent a cross between a normal kidney and a congenitally cystic kidney (the type with multiple small medullary cysts) and that the enormous dilatation of the tubules in the first patient may even have interfered with the development of the glomeruli which were extremely small and immature throughout.

DR. HOWARD G. WORTHEN: Dr. Barnett, we have not measured complement in these children. We have seen no other cases of mercury nephrosis. I was talking to Dr. Calcagno yesterday and he mentioned that he had seen one or two cases in which he thought mercury could be implicated. There have been a number of other cases reported in the literature, but, unfortunately, they are always like this one: a history of contact with mercury, or mercury demonstrated in the urine or tissues, and the patients develop nephrosis. That is the closest connection I can give you. Dr. Heymann, these 12 cases were accumulated during the period in which we saw about 150 cases of nephrosis in older children. In regard to the deficiency of podocytes in the normal newborn, the control I showed was from a child of about the same age as the infant with the infantile nephrosis. None of these cases were biopsied at less than 2 months of age. Control tissue obtained at autopsy in patients of this age have all shown normal podocyte development. We wondered about the location of so many cases in Minnesota, with a population of about three million, whereas in far more populous areas only one or two or a few cases have been reported. We have no explanation for this. Dr. Hallman reported eight cases from Finland. The reason for the relatively high incidence in that country is also not understood. In regard to Dr. Hansen's question about the familial nature of infantile nephrosis, Giles et al. reported infantile nephrosis in two siblings. The parents of these two children were first cousins, and the maternal grandparents were first cousins. This occurrence suggested to them that this was a recessive characteristic. We have seen some arterial changes in these infants' kidneys, even when the glomeruli appeared rela-

tively normal. We cannot interpret this finding. In the two children with chronic glomerulonephritis, arterial changes were seen also. In regard to Dr. Anast's question, we had one case with a low serum phosphorus. Phosphorus clearance was not measured in that case. We had one case with a very high serum phosphorus and a serum calcium of 4 mg. %. This was the first case of infantile nephrosis that we saw, so it was extremely confusing to us. This patient responded normally to parathyroid hormone, so we assumed that the changes in calcium and phosphorus were due to coincident hypoparathyroidism rather than to the renal disease. In regard to the cause of the low phosphorus and the increased phosphorus clearance, I would assume that this is very likely a tubular change. A case of typical Fanconi syndrome has been observed following nephrosis. In such cases, I would assume that perhaps the protein reabsorption affects the proximal tubule or a specific tubular abnormality accompanies some cases of nephrosis, causing decreased phosphorus reabsorption. Regarding Dr. Reiner's, Dr. Fomon's, and Dr. Guild's questions about the possibility of cystic disease, we considered this also. The kidneys of the other two patients with tubular dilatation looked much like the one shown here, but were not nearly so striking. The appearance in those cases did not suggest polycystic disease. In addition, we carried out microdissection of the kidneys in the case I showed you, and established that there was continuity of the tubule and that the cystic dilatation appeared to be localized to the terminal end of the proximal convoluted tubule. The area proximal to this was hypertrophied, not dilated. The areas distal to it appeared normal. We therefore consider that the tubular dilatation does not represent true polycystic disease of the kidneys.

12. Congenital Renal Tubular Acidosis. HAROLD E. HARRISON, M.D.; J. JULIAN CHISOLM JR., M.D.,* and HELEN C. HARRISON, Ph.D.,* Department of Pediatrics, Baltimore City Hospital, Baltimore.

Three cases of congenital renal tubular acidosis have been studied with respect to citrate metabolism, the response of renal tubular mechanisms to vitamin D, and the clinical and biochemical effects of treatment with excess cation. In each instance the patient was the only member of the family involved. In two of the three children nephrocalcinosis could be demonstrated by x-ray. One child had episodes of marked hypokalemia and all three had hypophosphatemic rickets. Renal clearances of phosphate were studied in one case and indicated marked impairment of renal tubular reabsorption of phosphate and it is assumed that the hypophosphatemia in all of the cases can be explained by this defect. Before correction of the acidosis, the hypophosphatemia was not influenced by moderate doses of vitamin D and a generalized aminoaciduria was also present. Following correction of the acidosis with either an excess of sodium or sodium plus potassium, the serum phosphorus rose to normal without increased vitamin D intake and the urine amino acid excretion also returned to normal. This suggested that the renal tubular mechanisms for reabsorption of phosphate and amino acids which are normally influenced by vitamin D were unresponsive to vitamin D during the phase of acidosis but showed a normal response when the acidosis was treated. All three of the children showed a uniform pattern of extremely low urinary excretion of citrate although plasma citrate levels were in the normal range. The urine citrate excretion remained low despite correction of the metabolic acidosis by sodium lactate or sodium and potassium citrate administration indicating that the alteration of renal tubular handling of citrate is related to the fundamental metabolic abnormality of the tubule cell. Treatment with excess sodium or sodium and potassium resulted in excellent healing of the rickets and acceleration of growth, but the urine citrate excretion remained exceedingly low, the polyuria persisted, and the nephrocalcinosis was unaltered.

Discussion

DR. ROBERT KLEIN, Pittsburgh: I wonder if Dr. Harrison could relate some of these changes to what happens when parathyroid hormone is administered to humans. I think that there are striking similarities, but what about the differences? I wonder, also, how far the pattern reaches. Dr. Fraser brought out that there are apparently so many variants to this wide spectrum that it is hard at times to distinguish one from the other. I wonder if Dr. Harrison would speak on this.

DR. WALLACE W. MCCRORY, Philadelphia: Dr. Harrison has mentioned the question about etiology. He did not mention, at least as far as I could hear, whether or not these children had infection. I would be interested in knowing whether there was associated urinary tract infection. Dr. Elkinton, in Philadelphia, has been carrying out some studies on patients (both adults and children) with renal acidosis. He did studies on five siblings of an adult with nephrocalcinosis. They were given an ammonium chloride load to test their capacity to respond to an acid load. He found that two of the five children showed a poor renal response to this acid load in respect to titratable acidity and ammonium excretion. I wonder if Dr. Harrison has done acid load tests of either parent or the other siblings.

DR. SAMUEL SPECTOR, Cleveland: I should like to ask whether the role of the parathyroid glands

* By invitation.

has not been too deemphasized by the authors? As an example, I should like to state our experience with a patient with a renal disorder similar to that reported. This was a 7-year-old boy, whom we have been following since the age of 6 weeks, with renal tubular acidosis and renal calcinosis. In the six months prior to his last hospital admission, the dosage of the sodium and potassium citrate mixture was inadvertently reduced and the child developed an increase in his renal calcinosis, a marked hypokalemia with generalized muscle paresis, florid rickets, and hypophosphatemia. His acidosis, however, was only mild. It was our feeling that the best explanation was that, during the period when he was not bolstered with an increased cation administration orally, the child lost an excessive amount of both potassium and calcium in his urine. The latter resulted in an increase in his renal calcinosis. This urinary loss of calcium also was responsible for a parathyroid hormone response which in turn increased his phosphate excretion and produced active rickets. All this seemed to occur while the child was receiving some citrate and did not have severe acidosis. This child, too, with an increase in sodium and potassium citrate mixture showed a prompt healing of his rickets and a return of serum potassium and phosphate to normal.

Dr. Howard G. Worthen, Minneapolis: Have you observed the opposite sequence of events, a reduction in the cation requirements when patients are treated with massive doses of vitamin D? Have you observed any changes in glomerular filtration rate from the pretreatment to post-treatment periods? I ask these questions because we have treated two patients with Fanconi syndrome who were extremely resistant to both vitamin D and sodium and potassium citrate. One of these patients was given 300 mEq. of cation per square meter without correcting the acidosis. When treated with massive doses of vitamin D, not only were the rickets healed, but also the citrate requirements fell to within a range of 20 or 30 mEq. per day. The aminoaciduria and glycosuria also decreased. These changes were accompanied by a decreased glomerular filtration rate after the vitamin D therapy. This demonstrated that the reduced excretion was due to reduced glomerular filtration, which reduced the amount of each substance filtered to a level which was within the ability of the tubules to accomplish reabsorption. We felt that vitamin D had no direct effect on the tubules. By analogy, this would suggest that the same thing holds for citrate treatment, that the acidosis itself may have no direct effect on tubular function.

Dr. Benjamin Kramer, Brooklyn: It has been previously shown that certain cases of refractory rickets fail to respond even to large doses of vitamin D. The bones of these patients are healed when an alkali or an alkaline ash diet is administered in addition. In these cases, large doses of vitamin D are required. I wonder whether Dr. Harrison was able to bring about healing with the normal therapeutic dose of vitamin D. If large doses were required even after the aminoaciduria was corrected, this would speak for some additional factor besides the acidosis as playing a part in the failure of calcification.

Dr. Malcolm A. Holliday, Pittsburg: In potassium deficiency with alkalosis, ammonia excretion is increased despite the fact that urine pH is elevated. Was there increased ammonia excretion in these children who had potassium deficiency, acidosis, and increased urine pH?

Dr. Harold E. Harrison: Dr. Klein, of course, has brought up the question of the interrelationship of parathyroid and vitamin D effect in tubular function, that is, in tubular regulation of serum phosphate levels. Albright, in his original description of a patient with nephrocalcinosis and rickets associated with what we now call renal tubular acidosis, suggested that the primary mechanism was depletion of body calcium stores due to hypercalciuria with secondary hyperparathyroidism. It is certainly not possible to exclude this possibility. Nevertheless, I do not think the evidence fits entirely with this hypothesis. Not all of these patients have marked hypercalciuria. They do not show other evidences of secondary hyperparathyroidism as far as the x-rays are concerned. In light of our inability to make any direct estimates of parathyroid activity, I think the question has to be left open. At the moment, there is no answer. About the variations in the spectrum of this syndrome, we are very interested in this, as there have been marked increases in the number of cases of renal tubular dysfunction reported in recent years. Some are called the Fanconi syndrome, some are called renal tubular acidosis, and some are given a variety of other names. Many of them show a considerable degree of overlap with respect to manifestations. Thus far, the only suggestion that we have to offer is that perhaps the abnormality of citrate excretion may be a specific differentiating point. We have not yet been able to study all the varieties of renal tubular dysfunction. It would be premature to say that the absence of citrate in the urine is specific for one particular type of renal tubular dysfunction. At the moment, however, we have not seen the absence of citrate excretion in any other type of lestion, except with this group of cases which we have described this morning. It may be worthwhile to do studies of urine citrate excretion in the wide variety of problems of renal tubular dysfunction. Dr. McCrory, none of these patients had any evidence of infection of the urinary tract. We have not studied the families as you suggested.

It would certainly be a worthwhile project. Dr. Worthen has suggested that the vitamin D therapy or the cation therapy might merely change the glomerular filtration rate. In one patient, the glomerular filtration rate was studied before and after treatment without evidence of change. There were no other evidences of disturbance of glomerular function in the other patients. We have not, certainly, enough quantitative studies, but I do not believe reduction of filtration could be the explanation for the marked increase in serum phosphorus which occurred rapidly as serum bicarbonate rose in these patients. The amount, Dr. Kramer, of vitamin D required to bring about healing in these patients is no greater than in the ordinary child with rickets if the acidosis is corrected. If the acidosis is not corrected, they respond poorly even to very large doses of vitamin D. When the acidosis is corrected, they respond almost immediately, even though no further vitamin D is given. Dr. Holliday, ammonia excretion was determined in the first case, but he did not have hypokalemia. His ammonia excretion was low at the time.

13. A Study of the Spectrum and Genetics of Nephrogenic Diabetes Insipidus. S. A. KAPLAN, M.D.*; A. YUCEOGLU, M.D.,* and J. STRAUSS, M.D.,* Department of Pediatrics, State University of New York, Downstate Medical Center, Brooklyn. Introduced by R. L. DAY.

A study has been carried out of members of three families in which diabetes insipidus occurred in eight persons. The following investigations have been made of the renal function of these individuals: glomerular filtration rate, urea clearance, urine osmolarity, ammonia production, and the titratable acidity and excretion of sodium, potassium, and amino nitrogen. The concentration in the plasma of the following substances has also been measured: total osmolarity, sodium, potassium, chloride, bicarbonate, pH, pCO_2 and urea nitrogen.

Since all of the subjects studied are related and since they all do not respond to vasopressin it is presumed that they all have the same disease. One of the most remarkable facts revealed by the study is the broad spectrum of the manifestations of this disease.

The most severely affected member is a little boy whose weight and height at 18 months are of the same approximate dimensions of a boy half as old chronologically. In addition to being markedly dwarfed, this child was found to have severe impairment of his powers of base conservation after being subjected to the test of administration of ammonium chloride for several days. Even more interesting was the finding of large quantities of amino-nitrogen in his urine during a period when his temperature was persistently elevated and when the concentrations of sodium and chloride in his plasma were high. Other members of the family, on the other hand do not appear to suffer from severe impairment of renal function other than a failure to respond to vasopressin and apparently subnormal ability to produce ammonia and hydrogen ions by the distal nephron. They have grown normally.

The disease appears to be transmitted by an autosomal dominant gene with incomplete penetrance.

The study is of interest first because it draws attention to the fact that familial nephrogenic diabetes insipidus is a syndrome which expresses itself differently in different families since the findings in members of this family appear to be different from those in the cases already reported. Since there are multiple defects of renal function in at least one member it appears unlikely that this is a disease syndrome in which there is a specific inborn error of metabolism with a deficiency of an enzyme system. It appears more likely that, in the persons described in this report, there is a predisposition to a more widespread lesion of the renal tissue which is genetically determined. Another interesting fact uncovered by this study is the occurrence of aminoaciduria during the period of growth retardation, suggesting the reasonable hypothesis that dwarfism in certain forms of renal disease is a consequence of loss of amino acids by the kidneys.

Discussion

DR. ROBERT L. BRENT, Philadelphia: There is no question of the existence of this disease in this report, but for that matter neither is there any doubt about the diagnosis in pedigrees with a slightly or greatly different pattern. This is not an unusual situation, namely, one apparent disease transmitted in a variety of ways. Retinitis pigmentosa has been reported to be transmitted as sex-linked recessive, recessive, and dominant. There exist several possibilities for the discrepancies with regard to this disease, aside from errors of past investigators. 1. There is more than one allele, which, when altered, can be responsible for the disease. 2. The sex-linked form of the disease can vary from recessive to dominant depending on the relative effectiveness of the "normal" remaining gene. The pedigree reported may be the dominant form, owing to the inability of the remaining gene to produce normality in the female. 3. Crossing over phenomena may change the nature of the pedigree. At the present time there is no way of proving any of these phenomena.

DR. ELEANOR COLLE, Minneapolis: We have had an opportunity to study one child in whom the defect is quite specific. He has no impairment of base conservation. Urinary citrate levels are nor-

* By invitation.

mal, and he has, on repeated examination, had normal urinary nitrogen with a normal amino acid pattern. Despite this, he has exhibited quite a marked retardation of longitudinal growth. We wonder if, at least, in some of these cases, this retardation might not be related to recurrent episodes of hyperosmolar dehydration or a related defect. The other thing that is very striking about this child has been a marked muscular hypotonia. I believe this has been reported in a number of other cases. It is unrelated to hypokalemia or potassium loss in the urine. I wonder if hypotonia was present in this family, and if Dr. Kaplan would speculate on the etiology.

DR. HAROLD E. HARRISON, Baltimore: The initial study, as I gather it, of the response of this child to ammonium chloride load was made while he was hypernatremic. Would this not be the explanation for his inability to conserve base while, subsequently, he showed a normal pattern of ammonia excretion and perhaps base conservation? In the rather rough renal function studies we have made in children during periods of hypernatremia, failure of concentration of urine and other evidences of renal dysfunction have been seen. Of course, there was a markedly decreased glomerular filtration rate with high blood urea nitrogen. It may be that this boy's inability to show base conservation was simply because the study was done at the moment of already existing hypernatremia. I think Dr. Kaplan has so charmingly presented the dilemma of the genetic aspect that it is hard to criticize what he has to say. Nevertheless, there do seem to be differences between the males and females. It is very different to see a child with persistent or repeated episodes of severe hypernatremia owing to severe water deficit in the first year of life, failure of growth, and, as Dr. Kaplan pointed out, so ill that one despairs perhaps of his life. At the other extreme is a woman, the mother of this child, who does have a defect of concentrating ability when tested by water restriction, but who gives no story of ever having been inconvenienced by her polyuria and no evidence of having been ill in infancy. Under these circumstances, I should think we would have to assume that this is not a simple dominant characteristic.

DR. WALLACE W. MCCRORY, Philadelphia: I would like to speak of the same point that Dr. Harrison has raised. I find it confusing to see the values of solute concentration achieved by these patients whom the authors call cases of diabetes insipidus. I would like to ask Dr. Kaplan to define the difference between true diabetes insipidus and the patient with some qualitative impairment of concentrating ability that may be resistant to correction by vasopressin but capable of elaboration of a hypertonic urine with proper stress. The two children we have observed with nephrogenic diabetes insipidus disturbances never put out a urine hypertonic to their own plasma even under conditions of severe dehydration. I am aware that Dr. Berliner has shown that you can elaborate a urine hypertonic to plasma in the absence of antidiuretic hormone, but the degree of hypertonicity is small compared to the values reported here.

DR. WILLIAM A. BRODSKY, Louisville: I should like to expand a little on Dr. McCrory's remarks. On the question of water deprivation with concentration of the urine above plasma; vasopressin sensitivity would present a fine case were it not for the alternative postulate made by Drs. de Wardener, del Greco, and Berliner recently. Let us consider the possibility that the kidney tubule may have a concentrating machinery operative in the absence of vasopressin. Then, water deprivation followed by concentration of the urine above plasma does not necessarily rule out vasopressin sensitivity or vasopressin resistance. I think this may be an important aspect of the question.

DR. LAURENCE FINBERG: I think Dr. Brent may have already said this, but I am not sure I understood him. As a nongeneticist, I wonder if the facts as I saw them might not better be explained on the basis of a sex-linked dominant?

DR. HOWARD G. WORTHEN, Minneapolis: We have observed a 13-year-old girl, who had not been seen by a doctor previously for her diabetes insipidus. This patient had spontaneously reduced her solute intake in an attempt to reduce her urine output by stopping the ingestion of milk six years previously. She was referred to us because of severe osteomalacia, which was corrected by resuming milk intake. In the management of these cases, if a decreased solute load is desired, it would be well to regulate the solute intake by omitting something other than milk, particularly in the young patients.

DR. S. A. KAPLAN: As far as Dr. Harrison's comments go, there are three other male members of this family who have the disease, in whom it is no more serious than in the females, so I still am going to plead for the recognition of the fact that this disease occurs in females. I am not going to get more involved than that. The sex-linked dominance of this disease is something that I would rather leave for those people who understand the machinations of the geneticists. As far as the comments of Dr. McCrory and Dr. Brodsky about the urine being hypertonic are concerned, there is no doubt about this in our patients. Our patients do produce hypertonic urine. The question of what the mechanism is, is something that I do not think we are in any position to speculate about. As far as the "small solute load treatment" goes, our patient who made such a remarkable recovery without any interference by his doctors, shows

that they can do very well occasionally without any therapy. We have been inclined not to interfere with the diet of the children. They have growth problems, and we feel that since their major problem is loss of solutes and loss of water, we ought not to provide them with more solutes and more water. Consequently, we let them eat as much as they please. We have not seen any hypotonia in our patients. The children are, if anything, quite muscular. Dr. Yuceoglu, who has done most of the blood collection, is not at all a muscular person and will attest to this. Dr. Harrison's comments about the hypernatremia as a possible cause of the poor base conservation are very well taken. This child was dehydrated and sick when we tested him. The observation of failure of base conservation in the presence of hypernatremia, however, was also made with children who have hyponatremia. I do not think our evidence would confirm the impression that it is hypernatremia which is responsible.

14. Renal Conservation of Base by Infants Fed Human Milk and Whole Cows' Milk. SAMUEL J. FOMON, M.D.*; DORRIS M. HARRIS, M.D.,* and ROBERT L. JENSEN, B.S.,* Department of Pediatrics, State University of Iowa, Iowa City. Introduced by Charles D. May.

Because whole cows' milk without additional carbohydrate provides the infant with a distinctly acid-ash diet while human milk provides a nearly neutral-ash diet, it seemed possible that infants of the two groups might have different abilities to withstand additional stimulus to conserve base. It was conceivable that the infant fed whole cows' milk might not be able to respond as well to the additional stress to conserve base imposed by infection, diarrhea, etc.

To explore this possibility, 24 studies of blood and urine have been carried out with eight infants under varying conditions. The mean total conservation of base (sum of titratable acidity and excretion of ammonia) in seven observations with five infants fed human milk was 8.0 mEq. per square meter per 12 hr. (range 6.2-12.1). After administration of ammonium chloride (4 gm. per square meter per 24 hr.) for two days, the mean total conservation of base in one observation with each of five infants was 25.1 mEq. per square meter per 12 hr. (range 21.7-29.6), an increase of 17.1 mEq. per square meter per 12 hr. resulting from the administration of the acidifying salt. Four infants fed whole cows' milk had a mean total conservation of base of 55.8 mEq. per square meter per 12 hr. (range 51.6-60.5) and, after administration of ammonium chloride to three of the infants, a mean of 79.3 mEq. per square meter per 12 hr. (range 68.5-87.6), an increase of 23.5. Thus, the chronic stimulus to base conservation of infants fed whole cows' milk did not interfere with ability to conserve additional base when a further stimulus was provided. The results of more prolonged administration of ammonium chloride are being investigated.

The studies resulted in several unexpected findings. Titratable acidity was responsible for more than half of the base conservation of the infants fed evaporated milk and, with the administration of ammonium chloride for two days, the increment in base conservation arose primarily from excretion of ammonia. Base conservation of infants receiving human milk and ammonium chloride was accounted for primarily (75%) by excretion of ammonia but, when two previously breast-fed infants were fed whole cows' milk for two days, the conservation of base was accounted for primarily by titratable acidity. An explanation for these findings will be presented.

Discussion

DR. SOLOMON A. KAPLAN, Brooklyn: The extraordinary thing to me is the demonstration of the added stress that the kidneys are subjected to when the infant is on artificial formula. The other extraordinary thing to me, from Dr. Fomon's evidence, is the ability of the neonatal kidney to adjust within the limits of the added stress. The question I would like to ask is whether, in the last slide, the relationship between phosphorus excretion and base conservation could possibly be artifactual and whether the load of phosphorus in the urine might be related to another factor, i. e., the increased total anion load.

DR. LYTT I. GARDNER, Syracuse, N. Y.: This, I think, is quite a tribute to the human infant's ability to metabolize so successfully milk from another species.

DR. HENRY L. BARNETT, New York: McCance has talked about the low rate of phosphate excretion making young infants more susceptible to acidosis. I wonder, in following the serum bicarbonates in these babies, whether there was any difference between the two groups. I also would like to comment upon what Dr. Kaplan said, by questioning the use of the word "stress" in terms of what the kidney is doing. I just think it is doing it. I am not sure it is being stressed.

DR. SAMUEL J. FOMON: In answer to Dr. Kaplan, I think it is possible that excretion of phosphate is related to base conservation indirectly rather than directly. In answer to Dr. Barnett, there was no difference in concentration of chloride in the blood either before or after administration of ammonium chloride in one group or between the two groups. The concentration was somewhat variable, but there was no pattern that could be detected.

* By invitation.

15. Skeletal Maturation and Dental Development. RICHARD WAGNER, M.D., and M. MICHAEL COHEN, D.M.D.,* Department of Pediatrics, Tufts University, School of Medicine, Boston.

It is still a debatable problem whether or not skeletal maturation and epiphysial development on one hand and dental development on the other are stimulated by the same factor. This question has been less intensively studied than the other components of development. Seckel called attention to the dissociation between chronological age, bone age, tooth age, sexual age, and mental age in cases of sex precocity.

Our own observations include five patients with idiopathic sexual precocity, four girls and one boy. The menarche in the girls occurred between 6 and 8 years of life; the boy showed far advanced extragenital sexual characteristics and testicular development at the age of 3 years. In all five cases, the eruption age of the teeth was consistent with the chronological age, whereas the bone development was far ahead and almost completed. Even after two years of regular menstrual periods the 12 year molars remained unerupted.

In contrast to the children with idiopathic sexual precocity, in three observations of adrenocortical sex precocity with excessive output of 17-ketosteroids the tooth eruption age was markedly advanced. One girl, first seen at the age of 7 years because of a benign adenoma of the adrenal cortex, had the two lower 12 year molars at 9 years of life; one girl with a malignant tumor of the adrenal cortex had a full set of decidous teeth at the end of the second year: one boy with adrenocortical hyperplasia had at 5 years his 6 year molars and two of his permanent incisors.

In view of the dissociation of genital and skeletal development, and tooth eruption it is to be expected to find in children with retarded skeletal differentiation a tooth eruption age consistent with their chronological age. This has been proved in many instances. It is not unusual to see for instance a child at 6 years who has the bone age of a 2-year-old child, but the chronological tooth eruption age. In cretinism both skeletal development and tooth eruption are simultaneously retarded, which does not prove the identity of the two respective stimulating factors.

Two conclusions can be drawn from these observations: 1. Skeletal maturation and tooth development are independent manifestations of development and do not parallel each other, whereas sexual development and skeletal maturation are concomitant; 2. Excessive excretion of androgens seems to stimulate tooth development.

* By invitation.

Discussion

DR. EDNA SOBEL, New York: I wonder if Dr. Wagner could give us some idea of the duration of the virilism in relation to the advance in dental development. I would expect acceleration in dental development would require some time for expression, as does acceleration of skeletal maturation. I have never observed advanced dental age in children with adrenal virilism. Perhaps we failed in this because we depended chiefly on the emerged teeth in evaluating dental development. As you mentioned, in boys with true sexual precocity the 17-ketosteroid excretion is not remarkably elevated, while in children with adrenal tumors or adrenal hyperplasia there is a pronounced elevation of the 17-ketosteroid excretion. In view of this rather uniform finding and the variations in dental development, it might be hazardous to rely on dental status in making a differential diagnosis between true and pseudo sexual precocity.

DR. FREDERIC N. SILVERMAN, Cincinnati: When I first read Dr. Wagner's abstract, I took advantage of our proximity to the Fels Research Institute to consult with Dr. Stanley Garn, who is their Director of Physical Growth. This accounts for my sudden erudition in this field which is probably a surprise to some of my friends and associates. I was interested in this field because I had been impressed by a study done by Prader and Perebo in 1952 on a large group of children with various types of endocrine abnormalities. These authors, on the contrary, decided that the teeth did not demonstrate any particular acceleration or retardation. However, they used radiographic standards. The radiographic standards used were those of Logan and Kronfeld. I think it is pertinent to point out that we must have good normative data before we can evaluate dental maturation. There are three phases in dental maturation, first, calcification, which apparently is not appreciably affected by endocrinopathies; calcification seems to be determined by some sort of "inner time," and there are very few things that can be done to children to make their teeth calcify more or less rapidly. Calcification can be studied in the living only radiographically. Eruption from the alveolus is the second stage, i. e., when the teeth break out of the alveoli. This too can be recognized radiographically. The third stage is gingival tooth eruption, a clinical observation. The two later stages are directly related to the endocrine states, and I think that the observations of Dr. Wagner on the acceleration in these children is a very helpful point along these lines. The disagreement with Prader and Perebo does point out, however, that we do need adequate normal standards. The original work of Drs. Kronfeld

and Logan was done on about 25 children. It was done primarily because Dr. Logan was interested in studying cleft palates and not dental development per se. At best, they are standards for beginning calcification. We now have good standards for gingival eruption, but for calcification and alveolar eruption, we do not. I hope they will be available soon.

DR. RICHARD WAGNER: As to Dr. Sobel's remarks I want to emphasize that we were driving in our study at the discrepancy between sexual and skeletal development on the one hand and dental development on the other. As an additional aid in the differential diagnosis between idiopathic and adrenogenic sex precocity, the evaluation of dental development can be of importance if the urinary 17-ketosteroid excretion is not excessive. In one of our cases with adrenocortical hyperplasia it amounted only to 6.8 mg. in 24 hours at the time the patient was first seen at 2 years of age and it rose only to 20 mg. in the course of further observation. I agree with Dr. Silverman that in view of the difference in the standards used by different investigators the statements in the literature on dental development are still controversial.

16. Diagnosis of Collection of Subdural Fluid by Transillumination. FREDERICK A. HORNER, M.D.*; N. C. WEBB JR., M.D.,* and KEASLEY WELCH, M.D.,* Departments of Pediatrics and Neurosurgery, University of Colorado, Denver. Introduced by Henry K. Silver.

The transillumination of the skull has long been helpful in the demonstration of abnormal collections of fluid in the cerebrospinal fluid pathways. We have found a modification of this procedure to be of value in demonstrating even minimal amounts of fluid in the subdural space.

A standard two-cell flashlight is modified by placing a narrow cuff of opaque sponge rubber about the illuminating surface. When this cuff is pressed against a flat surface, no light will be seen emitting from the source. When applied to the cranial vault of normal infants the foam rubber cushion allows for molding to the contours of the surface of the skull and only a very narrow rim of light is seen about the light source. This procedure must be carried out in a totally darkened room after allowing for dark adaptation.

One hundred normal children under the age of one year without C. N. S. disturbances were used as controls. Transillumination of the skull of the normal full-term newborn infant produced a rim of faint light which could be seen for a distance of 0.5-1.0 cm. about the rubber cone. Even less illumination was noted when the infant's hair was dark. Observations on 50 infants ranging in age from 2 weeks to one year showed a similar pattern, but with the rim of light extending to 1.5 cm.

In contrast to the circular faintly translucent narrow rim of light found in the 100 control infants, 10 children with subdural effusions that followed meningitis and 7 infants with subdural hematomas had areas of translucency which were brighter than those in the control group and extended out for a distance of from 2-12 cm. On three occasions, the areas of the translucency were noted over the temperoparietal area and subdural taps in the area of transillumination revealed abnormal collections of fluid, although preliminary subdural taps at the margin of the anterior fontanel had been negative.

On eight occasions transillumination was positive on one side and in all eight cases, bilateral subdural taps through the lateral margins of the anterior fontanel were productive of fluid only on the side that had shown an increased area of transillumination. In those cases where subdural effusions or hematomas were successfully treated by daily subdural taps, the areas of translucency decreased as the amount of fluid obtained diminished, and negative subdural taps were correctly anticipated by normal transillumination of the area.

When patients with fresh subdural hematomas were examined, abnormal transillumination was not noted until the character of the fluid changed from fresh blood to a diluted xanthrochromic fluid, usually a period of two to three days. With the exception of fresh subdural hematomas, accumulations of fluid were not demonstrated in patients who did not have abnormal transillumination.

It is felt that this test is of sufficient validity to make it a routine procedure in evaluating infants under one year of age suspected of having abnormal collections of fluid in the subdural space.

Discussion

DR. PHILIP R. DODGE, Boston: We have employed a technique almost identical to the one he described this morning for the past two years and have corroborated his findings in every way. In routinely using this particular technique in the evaluation of patients, we have uncovered 20 patients with abnormal degrees of transillumination. Four of this group of patients had subdural collections of the sort that Dr. Horner reported this morning. However, an additional 10 patients had a similar type of limited transillumination, but they were found, on exploration with a needle through the anterior fontanelle, to have increased amounts of subarachnoid fluid, which was of a different character than that found in the subdural space. The diffusion of light in both instances appears directly relatable to the distance between the surface of the brain and the inner surface of

* By invitation.

the cranium. One has, of course, to confirm the presence of and the character of the fluid, when present, by needle exploration.

DR. R. JAMES MCKAY, Burlington, Vt.: We, too, are very interested in this paper because we have been carrying out this procedure of examining infants with possible neurologic defects by transillumination for several years. We are now transilluminating all newborn infants who show any signs of neurologic abnormality, lethargy, or failure to feed well, and we have picked up a surprising number who have had either hydrocephalus, porencephaly, or hydranencephaly. This is an extremely valuable procedure in picking up central nervous system abnormalities among infants and should be particularly recommended as a routine procedure in the examination of newborn infants who may be candidates for adoption. Dr. Horner, have you tired transilluminating the occipital area in cases of postmeningitic subdural effusions? We know from autopsy evidence that these do occasionally occur in the occipital area, but we have never demonstrated them in the living patient. We have not had the opportunity of trying to do this since we have been using transillumination. I would also like to needle Dr. Horner a little bit on the statement he made that: "one cannot get the transillumination in the case of subdural hematomas for two or three days, that is, until the character of the fluid has changed from gross blood to the type which we ordinarily associate with this condition." Since a majority of his patients are postmeningitic subdurals, I would like to point out that most of us who have worked a lot with this condition think that they are effusions to start with and that the bleeding is secondary. I would suggest that the reason you have not seen transillumination early is that the fluid has not been there.

DR. FREDERICK A. HORNER: Dr. McKay, we have transilluminated, as you would suspect, all of our infants with meningitis, and we have transilluminated them over the entire skull. In fact, all of our flashlights are now kept with this sort of apparatus, and you cannot find one without it. We have not picked up any subdural collections in the occipital area. Most of them are temporal, parietal, and in the more traditional sites. We have picked up two in the frontal areas that were unsuspected. In regard to your remarks about the etiology of the subdural hematoma being an old effusion with frequent bleeding into it, we have felt that this was a possible explanation for many of these. It is difficult to prove, but I would agree with you that this does seem the likely explanation for the extremely poorly understood subdural hematoma.

17. Cineangiocardiography in the Study of Pulmonic Stenosis. F. N. SILVERMAN, M.D.; S. KAPLAN, M.D.*; E. MATTHEWS, M.D.*; K. EDWARDS, M.D.,* and G. CURRARINO, M.D.,* Department of Pediatrics, University of Cincinnati, College of Medicine, and The Children's Hospital, Cincinnati.

The availability of image intensification equipment for fluoroscopy has permitted the application of motion picture techniques to the study of the dynamics of cardiac abnormalities. Film exposure rates as high as 60 frames per second allow repeated slow motion study of contrast substance passing through the heart; features not appreciated by conventional "still" techniques can be clearly demonstrated by cineangiocardiography.

The greatest value has been realized when this method of examination is combined with cardiac catheterization. The catheter, the position of which is relatively safely followed by combining the image intensifier with closed circuit television apparatus, is placed in optimal relationship to areas of interest and movies are taken as contrast substance is injected at the selected site. The application of selective cineangiocardiography to the study of several forms of obstruction to the lesser circulation is the subject of this presentation.

Representative movies from a group of patients with pulmonic stenosis will be shown on a motion analyzing projector to demonstrate the following features.

1. Valvular pulmonic stenosis. The exact nature of the obstruction is shown in only 5 frames of film travelling at 60 frames per second. "Still" roentgenograms exposed at the rate of 10 per second could have bracketed, and thus missed, the diagnostic pattern. In addition, the irregularity of pulsations of the pulmonary artery are shown; these are thought to have diagnostic significance and can be identified on conventional fluoroscopy.

2. Isolated infundibular stenosis. The anatomical relationships of the muscular obstruction to a distal infundibular chamber and to the pulmonary valves are clearly defined.

3. Fallot's tetrad. In the atypical case, the diagnosis is established by demonstration of the area of stenosis and the unquestionably ventricular level of the shunt into the aorta. Moreover, the anatomical features of the pulmonary arteries are demonstrated for the planning of appropriate surgical therapy.

4. Hypertrophy of the crista supraventricularis in ventricular septal defect. It is not yet clear what significance of such hypertrophy is with respect to indications for surgical correction of the septal defect; but the presence of the crest can be recognized, and its stenotic effect shown.

* By invitation.

5. Tricuspid atresia. The small size of these infants permits viewing of the entire heart in the small (5½-in. diameter) viewing screen of the image intensifier. The sequence of filling of the several chambers is easily followed; filling of the pulmonary artery through a patent ductus arteriosus is clearly shown.

6. Transposition with pulmonary atresia. The anterior origin of the aorta contrasts with the previous examination; the septal defect is demonstrated, and the inability of the left ventricle to empty other than via the septal defect is made clear. Again a patent ductus arteriosus is shown.

Discussion

DR. GLEN CAYLER, Boston: Would you comment on the use of reversal film for this procedure? Did you make any effort to measure chamber pressure during the injection?

DR. F. N. SILVERMAN: We are using a 35 mm. camera to take our photographs and, in order to minimize radiation, we have to use very fast film. The Tri-X film which we are using has fairly large grain. If we use the regular negative film, we can then have positives printed and reduced to 16 mm. film of a very fine grain. We thereby reduce the size of the grain in the original negative four times. This gives us better definition on the projected film. However, we keep our original 35 mm. film as a master negative, and we never project it, because some time we may want to make another copy and review the material that we do have. As you can see, some of these films have been scratched in the course of our routine use. We have not measured intracardiac pressure during the examination. This has been done, I know, elsewhere.

18. Repeated Plasmapheresis in the Immunized and Convalescent Donor.† JOSEPH SMOLENS, M.D.; JOSEPH STOKES JR., M.D.; AGNES B. VOGT, M.D., and MARY N. CRAWFORD, M.D.

Plasmapheresis, or the obtaining from man of whole blood with retention of the separated plasma and the immediate return to the donor of his red cells, has been used only occasionally in the past.

The advent of the Cohn-ADC Fractionator with modifications introduced by one of us (Smolens) has made possible for the first time repeated plasmapheresis in the same person over the period of one year at biweekly intervals and under sterile conditions.

Three major uses have been immediately envisaged for such plasmapheresis with the same person: 1. Frequent plasmapheresis with the stockpiling of large quantities of sterile plasma by the use of relatively few donors. 2. The elimination of certain plasma constituents deleterious to health and life (poisons, excess of normal salts, or organic materials, etc.) and their replacement by normal plasma or by the same plasma improved by ion exchange resins or by other means. 3. The obtaining of quantities of convalescent plasmas or plasma from hyperimmunized donors for passive immunization and for therapy.

This report outlines the apparent value of the third use, particularly with respect to mumps, pertussis, and tetanus hyperimmune plasma, and to convalescent Rh and associated antibodies of sensitized mothers.

This method avoids the severe (about 50%) and occasionally fatal reactions to horse serum. It also takes advantage of the greatly increased efficacy of human antibodies over horse antibodies, unit for unit.

Data are presented which strongly suggest that biweekly plasmapheresis in the same hyperimmunized donors, even when more than double the total blood plasma is removed by this method within one year, stimulates continued antibody production at the original high level despite the absence of repeated parenteral injections of the specific antigen which are usually required.

Discussion

DR. IRVING SCHULMAN, New York: The technique of plasmapheresis has for me certain implications apart from the very interesting one Dr. Stokes has just pesented. I wonder, Dr. Stokes, if any studies have been made on other types of proteins, such as antihemophilic globulin, in plasma obtained in this manner. Also, what anticoagulant is used in this procedure?

DR. JOHN C. PETERSON, Milwaukee: In immunization studies which we carried out a few years ago in infants and also in adults, using tetanus toxoid as the antigen, we observed results similar to those reported by Dr. Stokes. That is, persons who had very high titers of antibody before immunization, whether the antibodies were actively or passively acquired, often responded poorly or not at all as compared with persons who initially had low titers of antibody.

DR. ROBERT A. GOOD, Minneapolis: I am very much interested in Dr. Stokes' observations from the standpoint of the theoretical basis of antibody production. I am sure you all realize these observations have broad implications in this area. I think, however, a word of caution is necessary. We have done similar studies, actually provoked by Dr. Stokes' visit to our laboratory, on experi-

† This investigation was supported in part by a Research Grant E-1191 from the National Institutes of Allergy and Infectious Diseases of the National Institutes of Health, Public Health Service.

mental animals. In these investigations we have used the quantitative immunochemical system to study immune response and have based our observations on responses to simple protein antigens. In contradistinction to the observations presented here, we could not demonstrate that plasmapheresis contributed to the maintenance of high levels of, or in any way prolonged, antibody production. It is difficult, of course, to transfer observations from the rabbit to the human, or from the type of plasmapheresis we used to the type you used, Dr. Stokes. Nonetheless, it is worthy of consideration that serial dilution methods of quantitating antibody have been notoriously misleading as a basis for measurement of the quantity of antibody produced. I do think that it would be extremely interesting if Dr. Stokes could extend his observations to other systems in which quantitative immunological determinations are possible, for example: pneumococcal polysaccharide, tetanus, or diphtheria toxoid, and to see whether or not the same results will be obtained, as has been the case with the agglutination titers.

DR. JOSEPH SMOLENS, Philadelphia: What volume of plasma did you remove from your rabbits?

DR. ROBERT A. GOOD: We were removing from rabbits of approximately 3 to 4 kg. body weight 50 cc. of plasma twice a week, which is a very large amount. I would have to calculate how this relates to the volumes of plasma removed from the volunteers, but I feel certain it would be at least as much as was removed in your experiments.

DR. JOSEPH SMOLENS: This is about 6%, which is about what we are removing from people.

DR. ROBERT A. GOOD: We tried to make it as similar as we possibly could.

DR. WILLIAM H. WEIDMAN, Rochester, Minn.: I would like to know if these methods have been used to study the effect of massive dilution, such as occurs during cardiac surgery using extracorporeal circulation.

DR. JOSEPH STOKES JR.: In answer to Dr. Schulman, we have used the sulphonated ion exchange resin on the sodium cycle, thus rendering the blood noncoagulable. This is used routinely prior to separation of red cells from plasma in plasmapheresis. The antihemophilic globulin is not altered by the plasmapheresis. About Dr. Good's comment, at the present time, dogs are being plasmapheresed to determine whether or not the same holds true in dogs as in human beings. The percentage of plasma that Dr. Good has removed from rabbits appears to be about the same as we have removed in humans. It is well recognized that there is a difference in antibodies from different species. There may be a difference in removal of antibodies with respect to whether or not plasmapheresis caused the titer to remain high. This, of course, has to be studied further.

19. Hereditary Enzymatic Defects as Illustrated by Hypophosphatasia. NORMAN KRETCHMER, M.D., Ph.D.*; MICHAEL STONE,* and CHARLES BAUER, M.D.,* Department of Pediatrics, The New York Hospital-Cornell Medical Center, New York. Introduced by S. Z. Levine.

There are many conditions which have been recognized and categorized as hereditary diseases, and these are particularly interesting to the biochemist and clinician, since they are usually associated with an anomaly in a metabolic pathway. Diseases in which the specific enzyme defect is known will be discussed briefly and a case of hypophosphatasia will be presented in detail.

Hypophosphatasia is an example of a hereditary disease where the associated enzymatic deficiency is detectable in the serum of the patient. This disease has been described in approximately 40 patients and is clinically characterized by a failure to thrive and faulty mineralization of bone in conjunction with negligible activity of serum alkaline phosphatase. Deficiency in activity of alkaline phosphatase was also observed in bone, liver, kidney, and intestinal mucosa.

The present report demonstrates that, after 18 hours of incubation, white cells stained with diazonium salt in the presence of naphthyl acid phosphate buffer give no indication of activity of alkaline phosphatase. In contrast, white cells from parents of the patient showed considerable evidence of alkaline phosphatase when examined histochemically. Functional tests such as the ability of the white cells to phagocytize sensitized pneumococci were normal in the patient. Activity of alkaline phosphatase in the serum of the parents was 0.8 to 2.7 Bodansky units and in the patient was 0.5 to 2.3 Bodansky units. Determination of the activity of alkaline phosphatase in white cells by a modified Lowry method yielded a neglible value with white cells obtained from the patient and values of .014 to .029μM of phosphorus liberated per hour per milligram of white cells from normal children. Addition of neither zinc nor magnesium to white cells of the patient was capable of activating the enzyme system.

Clinically, the patient improved markedly when administered cortisone and new calcification of bone was observed roentgenologically. There was, however, no effect observed on activity of either serum or white cell alkaline phosphatase. A three-stage craniectomy was done to relieve potential increased intracranial pressure.

Discussion

DR. EDNA SOBEL, New York: I wonder if Dr. Kretchmer could tell us whether the degree of hypercalcemia was improved at all by cortisone

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therapy. It is my impression that in the young infant with hypophosphatasia hypercalcemia is a major cause of symptoms, another cause being intracranial pressure. In the large number of patients that we reviewed, hypercalcemia was found only in the young infants. Beyond one year of life, hypercalcemia did not seem to occur at all. We have felt that hypercalcemia is not an integral part of the disorder, but rather that it might reflect the high calcium and vitamin D content of the diets given to infants.

Dr. Harold E. Harrison, Baltimore: I am interested in Dr. Kretchmer's interpretation of the cortisone effect is producing calcification. We have, I think, some independent confirmation of Dr. Kretchmer's thesis that the cortisone action is associated with cessation of growth. Calcification of rachitic cartilage, similar to that produced by healing of rickets, can be obtained by the administration of cortisone to rachitic rats in doses which inhibit growth. This calcification will occur under conditions in which the phosphate is reduced to extremely low levels and suggests that suppression of growth or growth manifestations in the cartilage does lead to some local change, which permits rapid concentration of bone mineral in the area. I should think that Dr. Kretchmer's thesis fits in perfectly with this.

Dr. Robert Klein, Pittsburgh: I would like to talk on the other side of this question, because we found that when we gave rats small doses of cortisone we increased the alkaline phosphatase levels of the serum. Then, when we went on to give large doses, we found a depressant effect. Similar rats were given parathyroid hormone and had all the usual findings of parathyroid poisoning. This could be prevented by giving cortisone during the same period of three days, which would suggest that growth recession was not a major factor.

Dr. Jerold F. Lucey, Burlington, Vt.: In 1956, Dr. Peter Scaglioni presented a case of hypophosphatasia before this society. The child has since been followed by Dr. Scaglioni and has received cortisone over a one year period without any change in the serum alkaline phosphatase or bone x-rays during this time. This child is older than the patient presented this morning, but it is interesting that there is apparently this difference in response to cortisone.

Dr. Blair E. Batson, Jackson, Miss.: We had a recent case in which we found low normal alkaline phosphatase activity in the patient and normal activity in the parents.

Dr. Donald Fraser, Toronto, Canada: I am particularly interested to learn that Dr. Kretchmer and his associates observed radiographic evidence of rapid bone healing when their patient was given small doses of cortisone. The rapidity of the improvement was comparable to that which we observed in a similar case. In our patient, the serum calcium levels fell appreciably during the early phases of healing, and (in contradistinction to Dr. Kretchmer's findings) the serum alkaline phosphatase activity rose toward normal from an average of 4 King-Armstrong units to between 8 and 10 units.

Dr. Norman Kretchmer: In answer to Dr. Sobel, we found an improvement in the hypercalcemia after the administration of cortisone. Dr. Klein, I think the point that Dr. Lucey alluded to, the question of the age of the animal and the age of your rats, might be pertinent in regard to alkaline phosphatase activity and the effects of cortisone. I would guess, and this is pure guess, that it would be difficult to raise the activity of an enzyme if the enzyme, in fact, is in some way different. For this, we obviously have no proof.

20. Erythrocyte Phosphate Metabolism in Infancy. Alvin Zipursky, B.Sc., M.D.* From the Departments of Pediatrics and Biochemistry, University of Manitoba, Winnipeg, Man., Canada. Introduced by Harry Medovy.

The red blood cell utilizes glucose to produce the energy necessary for its vital functions. The erythrocyte metabolizes glucose to lactic acid through a series of phosphate esters. These esters are soluble in trichloracetic acid and are usually referred to collectively as the organic acid soluble phosphorus compounds (OASP).

It was found that on incubation of whole blood of 23 adults for 5½ hours at 37 C there was a mean fall in OASP of 1.73 mg. % (S. D. ±1.76 mg. %). The erythrocytes of 16 newborns treated in the same manner showed a mean fall of 15.0 mg. % (S. D. ±6.41 mg. %). This increased rate of OASP disappearance would appear to be a characteristic of the red cells of the newborn as similar results were found when the erythrocytes of newborns were suspended in adult plasma or buffer. This rapid fall of OASP during incubation persists in the red cells of some infants up to at least 2 years of age.

2,3-diphosphoglyceric acid is present in high concentrations in erythrocytes of both adults and newborns. Studies in 6 adults and 8 newborns indicate that the fall in OASP is due primarily to a fall in 2,3-diphosphoglyceric acid.

The rapid fall in phosphate esters during incubation of newborns' erythrocytes may be due to an accelerated rate of breakdown, a decreased rate of synthesis, or both of these factors. To investigate this problem the formation of phosphate esters was inhibited by the addition of iodoacetic acid to blood of the adult and newborn. The disappearance rate of OASP under these conditions was similar in the two groups. This would suggest that there

* By invitation.

is no marked difference in the rates of breakdown of erythrocyte OASP in adults and newborns.

The transfer of P32 into the red blood cell is dependent on glycolysis and the formation of phosphate esters. In a series of seven adults studied, the mean rate constant of P32 influx was .237± .016 as compared with that of .175±.021 in five newborns. This indicates a significantly higher rate of incorporation of P32 into the erythrocytes of adults as compared with those of the newborn.

The nucleoside adenosine is able to supply energy to the erythrocyte through the hexose monophosphate shunt, bypassing the stages of glycolysis preceding the appearance of glyceraldehyde phosphate. The addition of adenosine to erythrocytes prevented the breakdown of OASP in both adult and newborn red cells and resulted in an actual increase in OASP.

These findings suggest that there is a difference in glucose metabolism between the erythrocytes of adults and newborns. This difference, which is evident on incubation, is present in the rates of build-up of phosphate esters. The slower rate in newborns may be due to relatively decreased activity of the early steps of glycolysis as compared with that in adults' red cells.

Discussion

DR. AUDREY BROWN, Detroit: I would like to know what the evidence is for a statement that I believe the author made to the effect that there is decreased reduction of glutathione in newborn red cells. We find increased reduction of glutathione levels in newborn erythrocytes. Has the author measured any levels in cord blood as opposed to erythrocytes in newborn infants in the first week of life?

DR. IRVING SCHULMAN, New York: It is very surprising to me that the changes described apparently persist until 2 years of age. Most of the recognizable differences between the erythrocytes of the newborn and of the adult disappear long before the age of 2. The red-cell population of the newborn has a younger mean age than in the adult and the individual red cells are thicker and, of course, contain fetal hemoglobin. I wonder if the author has studied the influence of these variables. For example, has he studied bloods in which there are large numbers of reticulocytes or in which the erythrocytes are thick, as in congenital spherocytosis, or in which the red cells contain fetal hemoglobin, as in thalassemia?

DR. ALVIN ZIPURSKY: Dr. Brown, to answer your second question first, all the original studies were done on blood obtained by syringe from the placenta. Later, we extended this to direct venipuncture from infants and children. Erythrocyte glutathione instability in the newborn has been reported by Zinkham and Childs and by Sheinberg et al.; these changes now appear to have been due to decreased blood glucose levels in the blood specimens of the newborns. Dr. Schulman has posed a number of very provocative questions. Initially we thought that the differences observed in the newborn would disappear in the first few months of life. Our studies would suggest, however, that these changes may persist up to 2 years of age. The reticulocyte count has to be considered in any specimen of blood examined for metabolic activity. In newborns it is higher than in adults, but this could not account for the large phosphate changes noted here. In addition, reticulocytosis would tend to cause an increase in the rate of P32 transfer rather than the decrease noted in newborns. Many of the younger infants had low reticulocyte counts, yet their blood also showed the phosphate changes noted in the newborns. Utilizing a technique similar to this, we have done some studies in hereditary spherocytosis and have found abnormalities.

21. Pseudo-Pseudo-Hypoparathyroidism as an Allelic Form of Pseudo-Hypoparathyroidism: Report of the Youngest Case, with Description of a Diagnostic Screening Technique.

ESTEN W. RAY, M.D.,* and LYTT I. GARDNER, M.D., Department of Pediatrics, State University of New York College of Medicine, Syracuse, N. Y.

This is a report of the youngest known case of pseudo-pseudo-hypoparathyroidism and the first child with the syndrome to be described in English. No cases of pseudo-pseudo-hypoparathyroidism had been reported in children until 1956 when two siblings were described by Seringe and Tomkiewicz in the French literature. In 1952 Albright et al. reported the clinical occurrence of short stature, round face, dyschondroplastic changes in bones of the hand and feet, and ectopic ossification, associated with normal serum calcium and inorganic phosphorus values. The remarkable prefix "pseudo-pseudo-" was adopted because in a previously described syndrome, pseudo-hypoparathyroidism, the above clinical findings plus convulsions had been associated with elevated serum inorganic phosphorus and depressed serum calcium concentrations.

The patient is a white girl, aged 7½ years, who was brought to the outpatient department because of retarded intellectual development and obesity. There was no history of tetany or convulsions. Physical examination revealed a very obese girl (91 lb.) with round face, strabismus, and stubby fingers. Her digits were short relative to the size of her palms. The finger nails were short and very wide, as were the toes. There were circular discolored bluish areas over the thorax, abdomen, and thighs. She was oriented, and would comply with simple requests, but was obviously mentally

* By invitation.

retarded. Laboratory data revealed normal values for serum calcium, magnesium, total protein, albumin/globulin ratio, and alkaline phosphatase activity. Serum inorganic phosphorus values ranged from 6.9 mg. per 100 ml. to 9.5 mg. per 100 ml. at different times. An Ellsworth-Howard test was negative, but the parathyroid extract used may not have been potent. Roentgenograms of the patient's hands revealed abnormally short, bowed metacarpals and short phalanges. Bone age was 13 to 14 years. There was soft tissue calcification in the feet, but none in the roentgenogram of the skull.

A thumb nail width/length ratio was derived by measuring the broad, short thumb of the patient (=2.8). Similar ratios obtained on a random sampling of children of similar age ranged from 1.1 to 1.4. A new case of this syndrome in an adult has recently been identified through the use of the thumb nail width/length ratio as a screening technique. It is suggested that the thumb nail width/length ratio be routinely included in the physical examination of children with convulsions of unknown etiology, in an effort to improve the identification of cases of pseudo-hypoparathyroidism.

The patient's mother had marked shortening of the 5th digit of each hand, with the site of the 5th knuckle replaced by a dimple. The mother's face was not especially round, and she appeared to be of average intelligence. Roentgenogram of the mother's hands showed shortening of the right 4th and 5th metacarpals and the left 4th metacarpal, with extensive soft tissue calcification in both hands and wrists.

Pseudo-pseudo-hypoparathyroidism and pseudo-hypoparathyroidism exhibit a genetic pattern reminiscent of diseases due to genes in the heterozygous state, i. e., so-called dominant genes. There is as yet no evidence that the two syndromes represent sex-linked genetic patterns. The findings suggest that pseudo-pseudo- and pseudo-hypoparathyroidism are two mutant alleles existing at the same locus.

Discussion

Dr. Robert Klein, Pittsburgh: I hate to carp after this elegant presentation of the syndrome, but I think, since the author has brought up the question of name, we can go into it further. I would call this pseudo-pseudo-pseudo-hypoparathyroidism, because I think it is actually the first syndrome described by Albright, or pseudo-hypoparathyroidism. I think the high phosphate level and lack of response to parathyroid hormone make it hard to classify this with the second group. However, this does bring up an important point that Dr. Ray and Dr. Gardner mentioned concerning the etiology. I would like to suggest that these cases probably present the same disease with different degrees of expression. This gets us back into a semantic morass in which we have been for several days over diabetes insipidus, diagnosis of hypercalcemia with normal serum calcium levels, and so forth. I know of no way out other than to take one name and say that it is Variant 1 or Variant 2, or something of that sort.

Dr. Edna Sobel, New York: I wanted to ask Dr. Ray about the stature of his patient, since it was not mentioned. If the child was not dwarfed, one would have to distinguish another form of pseudo-hypoparathyroidism. A patient that we are currently treating in New York shows skeletal dystrophy, mental retardation, and several other features of pseudo-pseudo-hypoparathyroidism, but his stature is superior. Dr. Klein mentioned that the plasma phosphate concentration of this patient was unusually high. Could some explanation of that be given? So far as the short metatarsal and short metacarpal are concerned, this manifestation of skeletal dystrophy apparently is not limited to pseudo-hypoparathyroidism in any of its degrees. I can think immediately of two patients with gonadal dysgenesis who had shortening of the fourth metacarpal bones.

Dr. Neil N. Litman, Los Angeles: The authors stated their fear of untoward reactions from the repeated use of parathyroid extract for phosphorus clearance tests. This is in conflict with Hiatt, who reported in the *Journal of Clinical Investigation*, 34:557, 1957, on repeated intravenous and subcutaneous injections of parathormone without reactions. Furthermore, he reported massive phosphorus diuresis even in normals given parathyroid hormone due to increased glomerular filtration. This would invalidate phosphorus excretion after parathyroid administration as a test for hypoparathyroidism. I wonder if Dr. Ray has any evidence for his statement that repeated parathyroid injections are dangerous?

Dr. A. M. Di George, Philadelphia: Before we start adopting the term "triple pseudo-hypoparathyroidism," I would like to mention our experience with a patient that we studied about a year ago. This was a 10-year-old child with normal stature, but with all of the characteristics of pseudo-pseudo-hypoparathyroidism as described by Albright. We failed to observe a phosphate diuresis following the intravenous administration of 200 units of parathyroid hormone. We were fortunate to have a patient with idiopathic hypoparathyroidism in the hospital at the same time, and administration of the same lot of parathyroid hormone to this patient produced an adequate phosphate diuresis. If my recollection serves me correctly, even Albright's first case of this disorder failed to show a phosphate diuresis with the usual Ellsworth-Howard test. The Ellsworth-Howard test, in our

hands and in the hands of many others, has not held up to the original promises of Ellsworth and Howard, in that one does not always obtain a phosphate diuresis in patients who are responsive to parathyroid hormone. This subject has been very completely reviewed by MacGregor in England. As far as simple diagnostic signs go, probably the very simplest sign that might lead one to suspect the diagnosis is the absence of knuckles. If the patient is asked to make a fist, one will note dimples over the metacarpal-phalangeal joints owing to the shortness of the metacarpals.

DR. ROBERT M. BLIZZARD, Columbus, Ohio: I would like to ask Dr. Ray if he measured fingernail ratios in gonadal dysgenesis patients. We have been using not the ratio per se, but the configuration, to assist us in the diagnosis of this condition.

DR. SYDNEY SEGAL, Vancouver, B. C.: Dr. Ray may be interested in one of Albright's original cases of pseudo-hypoparathyroidism, who was the first known patient with this disease to become pregnant. She delivered a child who lived for about two hours and died of causes which appeared to be obstetrical in nature or, at least, which could be explained on that basis. This infant showed at autopsy a peculiar bone architecture which defied any kind of diagnosis. The cord blood showed normal calcium and phosphorus levels. If this is a case of pseudo-pseudo-hypoparathyroidism, it may be interesting for Dr. Ray to write to Dr. Robert Neilsen of the University of Washington, who did the actual analysis.

DR. ESTEN W. RAY: Dr. Klein, I think, as I have indicated, that the nomenclature is in a bad enough state without my adding to it. You are quite correct in noting the high phosphorus, and I do not have any explanation for this. Factors which motivate against placing the child in the pseudo-pseudo- group are the normal calcium and the absence of history of convulsions or tetany, which factors, I think, are often very helpful and perhaps in some instances avoid the necessity of the Ellsworth-Howard test. Dr. Sobel, this child's stature at first appearance did actually appear short because of obesity. However, her weight places her at the 15th percentile. She is not as short as other cases of reported pseudo-pseudo-hypoparathyroidism. I have the same comments about the high phosphorus. I would agree with your comment about short metacarpals. This has been reported in this country and also in a notable family from England. Also, interestingly enough, with a familial tendency, a group of sisters all showed the disorder, but lacked, as nearly as I could see, the fingernail changes or other manifestations that you have described. In answer to the question of the dangerousness of the Ellsworth-Howard test, these were reports that were received by us, and I did not participate in the care or observation of either of these cases. One of the patients died.

22. Aldosteronism and Hypertension: The Influence of Complete Adrenalectomy upon Essential Hypertension in a Child. R. J. SLATER, M.D.*; D. W. GEIGER, M.D.*; J. LEESON,* and A. G. GORNALL, Ph.D.,* From The Research Institute of The Hospital for Sick Children, Toronto, and the Department of Pathological Chemistry, Faculty of Medicine, University of Toronto. Introduced by A. L. Chute.

This report presents for consideration the problems of management of severe hypertension (B. P. 220/180) of unknown etiology complicated by recurrent headaches, cardiac enlargement, gallop rhythm, and a trace of proteinuria in a 4-year-old boy. The possibility of a disturbance of adrenal function was questioned since urinary aldosterone excretion was increased to 12μg. per day (normal value for age 5, approximately 3μg. per day). No other signs of primary aldosteronism were present. The influence of dietary sodium in the blood pressure was studied during periods of normal sodium intake (68 mEq. per day) and of low sodium intake (8 mEq. per day). An immediate reduction in mean blood pressure from 186 mm. Hg to 100 mm. Hg occurred on the low sodium regimen; however, aldosterone excretion remained unchanged. The low salt regimen was not well tolerated. Intensive therapy with hypotensive drugs (reserpine, hydrolazine, and hexamethonium) decreased the mean blood pressure from 186 mm. Hg to 156 mm. Hg but was not successful in reversing the impaired cardiac state.

In view of the unsatisfactory response to medical management, surgical intervention was deemed advisable. Since the evidence implicated adrenal dysfunction, a left adrenalectomy was done in order to assess any beneficial influence. The excised gland was normal in weight and architecture. A temporary decrease in mean blood pressure (123 mm. Hg) as well as in aldosterone excretion 2μg. per day) occurred. The renal clearances of inulin and of paraaminohippurate, each of which had been decreased to approximately 60% of normal, increased to normal. However, cardiac enlargement persisted and, during the ensuing months, the blood pressure levels and aldosterone excretion (9μg. per day) increased and the renal clearances again became depressed. Consequently the right adrenal gland was removed; it also appeared normal. Thereafter, no urinary aldosterone excretion was detected, the mean blood pressure fell to 100 mm. Hg, and clearances again became normal, as did the cardiac size.

The boy is readily maintained on cortisone, 20 mg. per day, and 9α-fluorohydrocortisone

* By invitation.

(9α-F. F.), 0.05 mg. per day, without hypotensive therapy. Observations made during the nine months since adrenalectomy have revealed a marked sensitivity of the blood pressure to increases in intake of 9α-F. F. but not to sodium. This evidence suggests that the moderate increase observed in the urinary excretion and hence presumably in the circulating aldosterone may have been a factor in maintaining the severe hypertensive state. Despite a continuing mild hypertension, 125-130/90-100, there is no present evidence of adverse cardiac or renal involvement; the boy appears healthy and is developing normally.

Discussion

Dr. Henry L. Barnett, New York: I think all of us who have been faced with problems like this appreciate the turmoil produced by a patient of this type. I am interested particularly in whether or not renal function studies were done during the period when this boy was on the low-salt diet and during which his blood pressure did come down. If renal function was measured and came up to normal with the fall in the blood pressure, then one could ask whether or not the same good results that followed bilateral adrenalectomy might not have followed a prolonged period of severe salt restriction that you indicated it was not possible to carry out.

Dr. Charles H. Bauer, New York: Could you tell us whether renal biopsy was performed and, if so, what the condition of the kidney was? I am especially interested in knowing if the percutaneous and operative renal biopsy specimens were normal.

Dr. Frederic M. Blodgett, New Haven, Conn.: Inasmuch as it was this boy's personality that interfered with the trial or extension of low salt therapy, I wonder what observations were made regarding his personality in terms of his capacity to be adjusted or to be helped in a way that might make such therapy or some other possible.

Dr. R. J. Slater: Dr. Barnett, we had a difficult time making the final decision to remove the adrenal glands completely. With regard to your question about clearances carried out during the hypotensive phase of the low salt intake, I am sorry to say that such studies were not made. On the low salt regimen the boy failed to eat all of the diet provided and became lethargic, and, despite the decreased blood pressure, it became apparent that this regimen would not be successful. The gross appearance of the kidneys, seen at the time of operation, was normal. The percutaneous biopsy was carried out just prior to the second adrenalectomy and likewise revealed no evidence of architectural renal damage. With regard to the relationship of personality to hypertension, I can say that this was considered seriously. Dr. Elliot, the psychologist at our hospital, found the boy to be hyperactive with a short attention span and an average I. Q. of 100. On the basis of long-term observation it seemed that little would be achieved at this age with this particular boy in terms of therapy for a personality problem. Sedative therapy had been attempted initially, but it did not appear to influence the hypertensive state. It is of interest that one year after complete adrenalectomy there is little change in the boy's performance in the estimation of the psychoanalyst.

23. Effects of Drugs on Experimental Febrile Seizures: Development of a New Specific Therapy. J. Gordon Millichap, M.D.,* Department of Pediatrics, Albert Einstein College of Medicine, New York. Introduced by Henry L. Barnett.

In a clinical study of 114 patients with febrile seizures, the conventional methods of treatment were found to be inadequate. Acetylsalicylic acid and anticonvulsants administered either chronically or intermittently at the time of febrile episodes failed to prevent seizures in a large proportion of children. Status epilepticus in febrile patients required much larger doses of parenteral barbiturates than those found necessary in the absence of infection. The frequency of febrile seizures in pediatric practice and the concomitant neuronal damage which sometimes occurs emphasize the need for new and improved therapeutic agents with specific activity against this type of seizure. The ideal compound should have both potent antipyretic and anticonvulsant properties and should be nontoxic; its action should be rapid in onset and allow intermittent administration, so that chronic medication might be avoided when possible.

Febrile seizures were induced in mice by means of microwave diathermy generator. In animals between 3 and 4 weeks of age, a generalized seizure response was obtained when the body temperature was raised to 110 F. The threshold convulsive temperature was independent of the rate of temperature rise. The pattern of the febrile seizure was principally clonic in type; a tonic component observed at higher temperatures was mild, spasmodic, and unsustained. Various classes of drugs were tested for their ability: (1) to modify the threshold convulsive temperature, (2) to abolish the seizure completely, and (3) to retard the rate of rise in body temperature in the presence of the hyperthermic stimulus.

Antipyretics: acetylsalicylic acid and acetophenetidin failed to retard the rate of temperature rise and, in large doses, lowered the threshold convulsive temperature. Antibiotics: penicillin and oxytetracycline tended to increase the severity of the seizure pattern in some animals. Tranquilizing

* By invitation.

agents: chlorpromazine and reserpine were effective antipyretics, but had no anticonvulsant activity and no effect on the threshold convulsive temperature. Reserpine increased the severity of the febrile seizure pattern which became tonic extensor in type. Vasodilators: histamine and pilocarpine retarded the rate of temperature rise. Anticholinergic: atropine was both antipyretic and anticonvulsant. Anticonvulsants: trimethadione, meprobamate, and phenobarbital, of value in the treatment of petit mal and myoclonic epilepsies, were most effective in the control of febrile seizures, but large and toxic doses were required to abolish the clonus completely. Such drugs are also effective against the clonic metrazol-induced seizure. Diphenylhydantoin, which is ineffective against experimental metrazol seizures and in petit mal and is used primarily for treatment of tonic major seizures, failed to control the febrile convulsion and indeed, exacerbated the clonic pattern. Acetazolamide raised the threshold convulsive temperature but did not abolish clonus completely; it was also inactive against metrazol-induced seizures.

Several new compounds were screened first for their antimetrazol activity, and those most effective were selected for testing against fever-induced convulsions. Since barbiturates were particularly potent as antipyretics, related compounds were examined closely. A new barbital derivative (B. W. No. 401) proved remarkably effective against both metrazol- and fever-induced seizures. In addition, it was strongly antipyretic and its action was relatively rapid on oral administration. Compared with phenobarbital and metharbital, its toxicity was low and its protective therapeutic index (ratio of toxic to effective dose) was high. The new compound should prove superior to conventional anticonvulsants and should provide a specific therapy for seizures associated with fever.

Discussion

DR. FABIO SERENI, New York: I was very much surprised to see that the chlorpromazine did not change the seizures very much. This is mainly because in our data we showed that with chlorpromazine intracellular potassium fell as would be expected. According to the Millichap data, the seizure patient has been helped by chlorpromazine indirectly.

DR. J. GORDON MILLICHAP: Chlorpromazine has been known to exacerbate spontaneous seizures in certain instances. However, in animals with experimental febrile seizures, we were unable to show a lowering of the threshold in response to this drug. The change in cellular potassium concentration in the brain produced by chlorpromazine is of interest, but the significance of this observation in relation to the threshold to febrile seizures is not clearly defined.

24. Adaptations of the Newborn Infant's Cardiovascular and Pulmonary Systems to Extrauterine Life. FORREST H. ADAMS, M.D.; PETTER KARLBERG, M.D.,* and JOHN LIND, M.D.,* Department of Pediatrics, U. C. L. A. School of Medicine, Los Angeles, and Karolinska Sjukhuset, Stockholm, Sweden.

Information accumulated recently would indicate that the cardiovascular system of the normal newborn infant adjusts gradually over a period of several days rather than within minutes after birth as was previously supposed. Pertinent to the adaptive processes of the human infant's cardiovascular system are the obvious changes that must take place within the lungs. Too little is known at the present time concerning what happens to the lungs during the first few seconds and minutes of extrauterine life.

Two methods of study were chosen by us. In one group of mothers, the delivery was allowed to proceed to the point where the infant's head was just protruding, then a plastic tube was inserted into the esophagus and pressure recordings were made of the remainder of the delivery and through the first few breaths.

The second phase of the study consisted of taking rapid serial chest x-rays at the rate of four to six per second immediately following delivery. The following conclusions have been drawn from these studies on normal full term infants:

1. The process of normal vaginal delivery produces a moderate pressure effect on the infant's chest. Strong pulling can create pressures as high as 100 centimeters of water.

2. In most instances, immediately following delivery the chest does not recoil producing a large negative pressure. Thus there appears to be no "big squeeze" after-effect.

3. In slow breathers, a gradual rise in intrathoracic pressure is frequently observed prior to the first breath. We have no explanation for this; however, the observations are compatible with the theory of "capillary erection as a cause of lung expansion."

4. In most instances, expansion of the lungs occurs suddenly, particularly in the posterior parts, over a period of 0.15 seconds or less.

5. The first few breaths have a low pulmonary compliance, and the positive phase of respiration is very prominent. The range in pressures is from −70 to 100 centimeters of water.

Discussion

DR. CLEMENT A. SMITH, Boston: This is material that we have wanted particularly to know about. These measurements that Dr. Adams has given us on the positive pressures that take place

* By invitation.

when the infant is removed through the birth canal were not formerly available. I am not surprised that, however great the rebound negative pressure which follows, it does not usually coincide with the first breath, because that is what one observes. Now, as to the positive pressures which you have recorded, Dr. Adams, in the second or third breaths with the negative pressure of 15, 20, and 25 cc. of water or mm. of mercury (whichever it is) and the much higher positive than negative pressure; this, I suppose, means pressure against a closed glottis might tend to blow up the lung. Now, we have a group of young colleagues in Boston who submitted the paper listed as No. 90 on the program of the Society for Pediatric Research. Their work contains an attempt to answer this question of the effect of "capillary erection," which has interested a good many people. Drs. Avery, Frank, and Gribetz, working largely in the laboratory of Dr. Whittenberger at the Harvard School of Public Health, have measured the effect within the excised lung of increasing the pressure in the pulmonary capillaries by perfusing them under measured pressures. Briefly, when the pressure in the circulation of the excised lung was put up to approximately 60 or 70 cm. of water, the pressure in the lung, as recorded in the trachea, drops about 5 cm. In other words, when a pressure in the capillaries which might be equaled reasonably by the circulation following birth is created artificially, a small negative pressure is created in the lung. But this, as you will note in the abstract in the other program, is insufficient to move any air. Indeed as pressures which are large enough to move any air at all are produced in the capillaries, edema is formed. This, of course, would preclude the usefulness of the lung for respiration.

Dr. Sydney Segal, Vancouver, B. C.: I would like to compliment Dr. Adams and his colleagues on this wonderful work. I know that Dr. Clement Smith's group and a number of other people have tried to get such early measurements without this measure of success. I would like to ask Dr. Adams one question. As yet, has anyone shown by actual measurement that in the human newborn the pressure changes measured in the esophagus do provide an index of pressure changes within the intrapleural space? I ask this, realizing the controversy in adults and having had so far only one occasion recently to compare pressures in the two spaces in an anencephalic monster. In this first study, with two fluid filled systems, we did not obtain any promising results. However, this may not be a condemnation of the method. I wonder if Dr. Adams has any data on this subject.

Dr. Forrest H. Adams: I think it is very interesting to note that this method that Dr. Smith just described produces edema, because if this then takes place in utero it could be a mechanism for something like hyaline membrane disease. We made no studies that could answer his question.

Papers Read by Title

25. Congenital Coronary Arteriovenous Aneurysm. B. M. Gasul, M.D.*; E. H. Fell, M.D.*; M. Moreano, M.D.*; M. Weinberg Jr., M.D.,* and A. Gordon, M.D.,* Department of Pediatrics, University of Illinois, Chicago. Introduced by Heyworth N. Sanford.

Congenital coronary arteriovenous aneurysm with anomalous drainage into either the coronary sinus, the right atrium, the right ventricle, or the pulmonary artery is a rare malformation. We found 16 cases reported in the literature, 6 of which occurred in patients under 16 years of age. In none of these patients was a clinical diagnosis made, and none of them have had angiocardiograms taken. Six of these sixteen patients underwent a thoracotomy with the preoperative diagnosis of patent ductus arteriosus in four, aorticopulmonary fistula in one, and an arteriovenous fistula, site undetermined, in another case. Of these 6 patients 3 had a successful corrective surgical procedure, and in the other 3 no attempt was made to correct this anomaly.

We wish to report on an additional three patients with an aneurysmally dilated right coronary artery draining into the right ventricle, who have had an angiocardiographic and physiologic studies, and 2 of whom were correctely diagnosed before surgery.

Case I.—A noncyanotic 7-month-old boy was diagnosed clinically as a case of an arteriovenous coronary aneurysm. This diagnosis was confirmed by venous angiocardiography and cardiac catheterization. Corrective surgery was successfully accomplished.

Case II.—A 3-year-old boy was diagnosed as a case of a congenital rupture of the right sinus of Valsalva on clinical, retrograde aortography, and cardiac catheterization findings. At operation this diagnosis was shown to be incorrect and the aneurysmally dilated right coronary artery that entered the right ventricle was successfully ligated, and the aneurysm was resected.

Case III.—A white boy, 9 years of age, who was diagnosed by us three years ago as a case of congenital rupture of the right sinus of Valsalva on the basis of clinical findings, venous angiocardiography, retrograde aortography, and cardiac catheterization, was restudied recently. Because of our experience with Case II, our diagnosis was changed to an aneurysm of the right coronary artery draining into the right ventricle. This was proven at operation and a successful corrective procedure was accomplished.

* By invitation.

Slides illustrating the salient points of the pre- and postoperative clinical, angiocardiographic, retrograde aortography, and physiologic findings will be presented. We believe that for the first time the correct preoperative diagnosis can be demonstrated on patients with these malformations by correlating the clinical and angiocardiographic findings, and that corrective surgery is feasible for these patients.

26. A New Inborn Error of Fatty Acid Metabolism. JOHN A. BIGLER, M.D.; ROLAND MAIS, M.S.,* and DAVID YI-YUNG HSIA, M.D.,* The Children's Memorial Hospital, Chicago.

The present report concerns a new clinical syndrome characterized by hepatomegaly, retardation of physical and mental growth, and a disturbance of fatty acids in the plasma.

The first affected child is now nearly 10 years old. At about 6 months of age, he was noted to have an enlarged liver, which has persisted up to the present time. The spleen has never been palpated. The patient has never been jaundiced, has never had dark urine, and has not presented symptoms of liver disease at any time. Physical growth has always been slow. At 6 years of age, his weight was 36 lb., his height, 39 in. At 9½ years of age, his weight was 38 lb. and his height, 44 in. Bone age was also markedly retarded. I. Q. was a low normal of 72. Various carbohydrate tolerance tests were within normal limits and liver biopsy showed no evidence of von Gierke's disease. Treatment with thyroid extract and Saafflower have been without effect.

One other sibling, aged 5, shows identical clinical and laboratory findings. Six other siblings are perfectly normal and well. The parents are second cousins.

Routine plasma fat studies in the affected children revealed the changes, expressed as mg. %, shown in the Table.

	Normal Range	Patient 1	Patient 2
Total lipids	570-820	1,377	984
Total cholesterd	110-300	208	197
Cholesterd esters	35-90	96	119
Phospholipids	170-330	497	335
Triglycerides	170	606	370
% Cholesterd esters	70%	46.1%	60.4%
Cholesterol phospholipids	0.95	0.42	0.59

Paper electrophoresis of the plasma proteins revealed a normal pattern. However, parallel studies for lipoproteins revealed an almost total absence of α-1- and β-lipoproteins. Instead, there was a prominent peak at the α-2 position consistently.

The plasma was also subjected to potato starch electrophoresis by the technique devised by Kunkel. After electrophoresis was completed, the bed was sectioned into 1 cm. wide zones and extracted with 10 ml. chloroform-methanol (2:1) and each segment was redetermined for cholesterol, phospholipids, and triglycerides. The details of these studies will be described.

It would appear that we have identified a new inborn error of fatty acid metabolism. The condition is probably transmitted as an autosomal recessive and represents a defect in the conversion af an α-2 lipoprotein in the body.

* By invitation.

27. Chronic Renal Disease in Children With Lipodystrophy. SYDNEY S. GELLIS, M.D.; SIDNEY GREEN, M.D.,* and DOUGLAS WALKER, M.D.,* Departments of Pediatrics, Harvard Medical School and the Boston University School of Medicine, and the Children's Medical Center, Boston.

The clinical picture of progressive lipodystrophy is a well established one. The first case to be described in the medical literature was by S. Weir Mitchell in 1885, and the disease has been retrospectively reported in an Egyptian pharoah. The condition most frequently begins in childhood, usually between the ages of 4 and 8 years, although a fairly large number of cases begins during puberty. It has been reported twice as often in females as in males and usually appears insidiously in the face with progressive painless disappearance of subcutaneous fat, remaining confined to this area or spreading downward to involve the neck, shoulders, arms, and thorax. Several months to years may be required before the process is complete. In some patients an increase in subcutaneous fat of the lower portion of the body is described but this does not occur regularly and may be due to an unsuccessful attempt by increased caloric intake to overcome the distressing facial appearance. In rare instances lipodystrophy has involved the lower extremities rather than the upper portion of the body.

It is generally stated that other systems are essentially normal and that patients with lipodystrophy have an excellent prognosis with regard to life expectancy.

Various theories regarding the etiology of lipodystrophy have been proposed: infection, endocrine disturbance, and central nervous system lesions, but no suggestions to date have received general acceptance.

A review of 12 cases seen at the Children's Medical Center has yielded unusual data with regard to renal disease in patients with lipodystrophy. Of the 12 cases, 7 were female, 5 were male. Seven (four males, three females) of the 12 have shown evidence of renal disease; in one case, chronic nephritis has followed allergic purpura, in five,

acute glomerulonephritis has become chronic, with death from chronic nephritis occurring in three of the five. The seventh patient has pyelonephritis with recurrent hematuria and hydronephrosis. Thus, of the seven patients, four have chronic renal disease, and three have died as a result of renal failure.

A review of the extensive literature on lipodystrophy (which includes approximately 150 cases) reveals only four patients who appear to have had associated renal disease, and the high incidence in the present series is therefore of unusual interest, strongly suggesting that the two conditions are related and not coincidental. An attempt will be made to correlate the two.

The present series will be discussed in detail, and autopsy findings will be reported.

28. The Metabolism of Substance S in Children and Adults. ALFRED M. BONGIOVANNI; WALTER R. EBERLEIN,* and JOAN L. CADDELL,* Department of Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia.

The elevation of urinary 17-ketosteroids occurring during pubescence has been attributed to the increased secretion of adrenocortical androgens, and testicular androgens in the male. Meanwhile the urinary corticoids remain constant throughout life, on the basis of body surface area. Talbot suggested that a "second" ACTH, which specifically stimulates adrenocortical androgens, enters the picture at the time of puberal development.

The administration of Substance S (a C-21 steroid) to 12 normal adults produced a rise in 17-ketosteroids accounting for 4.7% of the dose, and the rise was attributed to the urinary excretion of etiocholanolone, a metabolite of Substance S. On the other hand, 13 children showed a rise in 17-ketosteroids, accounting for only 1.3% of the dose. The difference was significant. Other variations in metabolism were also noted.

These results suggest an alternate explanation for the rise of 17-ketosteroids at adolescence. The enzymes which degrade C-21 steroids are postulated as increasing with the attainment of maturity, so that a portion of the elevated 17-ketosteroids are derived from the metabolism of larger molecules, rather than entirely *sui generis*.

The various urinary products occurring after the administration of Substance S have been isolated and identified. Differences between the metabolism of hydrocortisone and Substance S have also been noted.

* By invitation.

29. The Effect of Adequate Hormone Therapy in Active Carditis with Special Reference to the Duration of Therapy. MAY G. WILSON, M.D., and WAN NGO LIM, M.D.,* Department of Pediatrics, The New York Hospital-Cornell Medical Center, New York.

In our previous studies it was reported that overt residual cardiac damage was not observed in patients with progressive symptoms and signs of active carditis who had received early adequate hormone therapy for an average period of seven days. In the majority of recent reports comparable observations have been made, although after the first week therapy was continued in minimal amounts for periods of three weeks to three months or more.

This study is concerned with a comparison of the effects of adequate short-term steroid therapy in 45 patients with carditis of varying duration. In addition, the gross and microscopic findings in 38 patients with symptoms and signs of active carditis who received symptomatic therapy were reviewed.

It was observed that in the majority of patients receiving steroid therapy, with carditis of less than two to three weeks' duration, there was termination of the symptoms and signs of active carditis by the end of one week of therapy without overt clinical evidence of residual cardiac damage. In patients, with active carditis of one to three months' duration or longer, residual cardiac damage was not prevented, although progressive symptoms and signs of carditis were arrested.

Among the 38 patients who had received symptomatic therapy, the carditis was of one month's duration or less in 19, one to three months' in 13, and in 6 the duration was three to six months. An acute inflammatory process involving the various cardiac structures was found at necropsy irrespective of the duration of symptoms of active carditis. It is significant that irreversible cardiovascular damage was only minimal in those with carditis of one month's duration or less, in contrast to the extensive irreparable lesions found in patients with carditis of one to three months' duration or longer.

In view of the potential hazards of long-term hormone therapy, the advisability of continuing therapy in the absence of clinical evidence of active carditis will be discussed in terms of the pathological findings presented.

It is concluded that adequate hormone therapy is indicated only in the presence of progressive symptoms and signs of active carditis. In the majority of patients, effective hormone therapy need not be continued for more than one week.

30. Nephrotic Syndrome in Children, Observations Over a Period of 32 Years. JEROME L. KOHN, M.D., and DONALD GRIBETZ, M.D.,* Department of Pediatrics, Mount Sinai Hospital, New York.

Data are reported concerning 81 patients with childhood nephrosis some of whom have been observed personally for 32 years. These observations are presented to add to the understanding of the natural history of the syndrome and to offer a basis for the comparison of results of older methods of therapy with those which have been introduced during the past few years.

Patients have been grouped into three categories: Group I, 33 patients whose illness began before antimicrobial agents were available; Group II, 24 patients who became ill after the advent of antimicrobial drugs, and Group III, 24 patients whose onset of illness occurred after the introduction of pituitary and adrenal hormone therapy. The latter group was treated with hormones and antimicrobial agents.

The groups have been compared as to mortality. Group 1: 21 patients (64%) are known to be dead, 17 died within the first year after onset, mainly of infection, and the remaining 4 within three years. Group II: 15 patients (63%) are known to be dead, 5 within the first year and the remainder within four years, mainly of chronic nephritis. Group III: four patients have thus far died within two years of onset. If to these are added three patients who have symptoms of irreversible renal disease and who may die within four years of onset, the combined mortality would be 29%.

The first 24 months after onset were arbitrarily selected, in an effort to assess the effect of hormone therapy on duration of edema. Groups II and III were compared. The average number of months of edema in 24 months was 18 in Group II, whereas it only averaged 6 months in Group III.

Finally the present condition of the living patients was ascertained. Group I: Of the 12 survivors one has been lost sight of. The remainder have been followed 15 to 32 years. Six patients have been seen during the past year. All are in good condition clinically and lead normal lives. Four have albuminuria. The blood pressure and blood chemistries are normal in all but one patient, who has minimal nitrogen retention coexisting with diabetes. Group II: Of the nine survivors, two have been lost sight of, while seven followed from 10 to 14 years and have been examined within the past year. Five of these patients are clinically well, although three of them have slight to moderate albuminuria. One patient has chronic renal disease, and one has recently had a recurrence of edema. Group III: 20 patients have been under observation from 8 months to 8½ years. Ten are clinically well, four of whom have albuminuria. Seven are in good condition but still under treatment; all seven have albuminuria. The three remaining patients have irreversible renal damage.

Tentative conclusions are (1) that prior to the introduction of combined hormonal agents and antimicrobial therapy, approximately one-third of patients with childhood nephrosis could be expected to survive and lead active useful lives despite the persistence of albuminuria, and (2) that the present hormonal regimens favorably influence the morbidity by definitely decreasing the duration of edema and thus far exhibit an apparently favorable influence on the case fatality rate.

31. Acute Respiratory Diseases During Infancy and Childhood: I. The Incidence of Infection With Adenoviruses. HERBERT A. WENNER, M.D.; T. D. Y CHIN, M.D.,* and ALICE MARSH, M.D.,* Department of Pediatrics, University of Kansas School of Medicine and the Kansas City Field Station, United States Public Health Service, Kansas City, Kan.

The association of adenoviruses with several discrete clinical syndromes pertaining to the respiratory system has prompted studies on the risk of infection with adenoviruses. A study has been in progress for two years embracing 168 families resident in the Command and General Staff College at Fort Leavenworth, Kansas. The family unit was studied in order to appraise the dispersion of adenoviruses within the aggregate, as well as in the community. Blood samples were obtained in the early fall and summer months for determination of changes in antibody status during the respiratory season. Nasal and oropharyngeal exudates were obtained during respiratory infections for virus studies.

Five cytopathogenic agents were detected in 187 specimens obtained from 153 individuals. Four viruses were recovered from infants and young children. Two were adenovirus Type 2 and two were adenovirus Type 3. The remaining agent, recovered from an adult, has not been identified. Homotypic antibodies emerged in patients from whom viruses were recovered. Serologic studies revealed that adenoviruses Types 2, 3, and 5 tend to disperse widely in the family unit. The capacity of these three adenoviruses to involve all or most members of a family indicated a greater dispersal rate than was observed for other adenoviruses studied.

During the past three years additional studies have been made on 67 normal infants and 72 children admitted to the Children's Hospital. The infants were recruited from a nutritional study group where they were observed from the newborn period to at least one year of age. Seroconversion against adenoviruses occurred twice in the infant

* By invitation.

group. The sick children entered the hospital because of spasmodic croup, bronchiolitis, or undifferentiated respiratory illnesses. Intensive studies have been made to detect viral agents by tissue culture methods and to obtain serologic evidence of infection with adenoviruses, croup, JH, and influenza A, A′, B, C, and D viruses. Bacteriologic studies have been carried out also, particularly, the role of H. Influenzae Type A, and pneumococci in tracheobronchitis, and bronchiolitis. Except for recent recoveries of influenza virus, other viruses have been encountered twice. Neither is adenovirus. One resembles croup virus; the other is unidentified.

These studies emphasize the need of better methods for the detection of viruses causing undifferentiated respiratory infections. Adenoviruses Types 2 and 5, and probably Type 3, may be responsible for about 15% of undifferentiated respiratory infections during infancy and childhood. Since adenoviruses have not been found in the clinical syndromes mentioned they are associated most often with minor respiratory illnesses.

32. The Effects of Cortisone Acetate on Intradermally Induced Vaccinia Infection in Rabbits. LAWRENCE M. BUGBEE, M.D.*; ROBERT B. STEWART, Ph.D.,* and ARTHUR A. LIKE, M.D.,* Departments of Pediatrics, Bacteriology, and Pathology, University of Rochester School of Medicine and Dentistry, Rochester, N. Y. Introduced by William L. Bradford.

Procedure.—Ten New Zealand white male rabbits were treated with 15 mg. cortisone intramuscularly every day for 12 days. An equal number of control rabbits receiving saline were observed simultaneously. Each group was inoculated intradermally with 0.1 cc. of a 10^{-5} dilution of stock vaccinia virus and observed for changes in temperature, weight, blood, sugar, total white blood cell count and differential, and symptomatology. In addition changes in gross and microscopic appearance of site of inoculation in skin, liver, spleen, and brain, were investigated. Finally serial ten fold dilutions of blood, liver, and spleen were inoculated onto the chorioallantoic membrane of 10-day embryonated hen's eggs and the amount of vaccinia virus in each organ quantitated.

Results.—(*A*) General. Five of the cortisone-treated rabbits died with antecedent symptoms of encephalitis. From two others that were killed vaccinia was recovered from brain tissue. Only one of the control rabbits died, and at autopsy an unassociated bronchopneumonia was found. None of the controls developed encephalitis.

There was no significant difference between the two groups with regard to changes in weight or total white blood cell count. The antipyretic effect of cortisone was demonstrated. The antilymphocytopoietic effect of cortisone was illustrated by the decrease in total lymphocytes in the peripheral blood as well as the changes in microscopic appearance and gross size of the spleen. The hyperglycemic effect of cortisone was also demonstrated.

(*B*) Virus Titration. Virus was recovered from the bloodstreams, livers, and spleens of both groups. In the cortisone-treated group, however, the titers of virus were much higher than in the control group. The increase in virus titer also corresponded in time with the period in the experiment where the death rate was the highest. Virus was recovered from the brains of all seven cortisone-treated rabbits that died or were killed after the third day of infection. No virus was recovered from the control brains.

(*C*) Pathology. Gross and microscopic changes were observed in the skin, liver, spleen, and brain. In the skin of the cortisone-treated group there was a marked diminution in inflammatory response. The livers of the same group showed progressive focal necrosis with only minimal inflammatory reaction. The necrosis had no specific pattern and involved large areas scattered throughout the liver. Grossly the liver was covered with punctate pale areas of destruction. The only microscopic changes found in the livers of the control rabbits were in the form of a few chronic inflammatory cells located in the periportal areas. No disruption of hepatic architecture was seen. The spleens of the cortisone-treated group showed diminished numbers of lymphocytes and some increase in connective tissue. The brains of the same group showed prominent neuronal degenerative changes with occasional perivascular cuffing of lymphocytes. Inclusion bodies were not found in any of the organs of either group. No changes were observed in the spleens of the control group; however, sections of brain showed an occasional mild perivascular lymphocytic infiltration.

(*D*) Conclusions. From the data obtained it appears that cortisone has a definite enhancing effect on vaccinia infection in rabbits.

33. Antibiotic Prophylaxis of Bacterial Complications in Measles. SAMUEL KARELITZ, M.D., and HENRY D. ISENBERG, B.S., M.A.,* Department of Pediatrics and Laboratories, Long Island Jewish Hospital, New Hyde Park, N. Y.

The problem of prophylactic use of antibiotics against complications of measles has been investigated in the past with conflicting results cited in the literature. The present investigation had as its objective the clarification of these contradictory findings.

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Two hundred cases of measles were studied. Sixty-six patients were hospitalized; one hundred thirty-four remained at home under the supervision of staff pediatricians of The Long Island Jewish Hospital. Of the entire group, 138 were treated with antibiotics; 62 did not receive any. Further groupings of complicated and noncomplicated were made. The time of the development of complications with respect to treatment constituted an additional category.

At the onset of symptoms of measles, nasopharyngeal cultures were obtained. These were repeated 1 week to 10 days after the original culture was taken. A detailed bacteriological analysis was made. Anaerobic, microaerophilic and aerobic isolations were attempted with all specimens, and the isolated organisms were identified according to accepted bacteriological criteria. Antibiotic profiles against 12 different antibiotics were established for each isolate. Comparison of the effect of treatment on the microflora of the nasopharynx was then possible. In addition, all coagulase-positive Micrococcus pyogenes var. aureus were typed via bacteriophage technique. Concomitantly, each physician reporting the measles documented his findings and treatment, listed the onset and duration of complications, and when necessary, submitted additional cultures for laboratory study.

Twenty-one different microorganisms contributed to the microflora of the measles patients. Some of these bacteria were encountered only occasionally, while organisms such as the viridans streptococci occurred with great regularity. In a few patients, no change in the microflora occurred with treatment, while in many, a different group of organisms was isolated after the specified time interval. This observation was applicable to treated as well as untreated cases. Treatment frequently changed the antibiotic profile of resident microorganisms but occasionally even untreated patients yielded bacteria, particularly staphylococci, with changed antibiotic susceptibility.

All staphylococci from patients remaining at home which were identifiable by bacteriophage lysis were typed. No pattern implicating any particular bacteriophage strain evolved, although the observation that penicillin-resistant micrococci differ from their susceptible relatives in bacteriophage type was borne out. The concept that penicillin-resistant staphylococci colonize the nares, after the destruction of susceptible strains, can be extended to the nasopharynx in patients afflicted with measles. The paucity of β-hemolytic streptococci, pneumococci and Hemophilus influenzae in the nasopharynx of both the treated and nontreated group is striking but real, since two entirely different laboratories were engaged in investigating this aspect of the study.

Although the larger number of patients received antibiotics, only four complications occurred following antibiotic therapy. These complications were amenable to antibiotic treatment, making a conclusion of causal relationship between therapy and appearance of the complication difficult. All other complications reported here were present at the onset of treatment at home as well as in the hospital, and all but the encephalitides responded well to the various antibiotics employed.

The complications encountered in the series studied included bronchitis, otitis media, pneumonia, encephalitis, and meningitis. It is noteworthy that of the hospital children, a greater percentage was in the 1 to 3 year age group than among the children treated at home. It is obvious from the distribution of the complications that these children were admitted to the hospital because of the complications, many of which might have been prevented by antibacterial prophylaxis.

34. Phenoxymethyl Penicillin in the Treatment of β-Hemolytic Streptococcal Infections. MAXWELL STILLERMAN, M.D.,* and STANLEY H. BERNSTEIN, M.D.,* Pediatric Research Laboratory, Long Island Jewish Hospital, New Hyde Park, N. Y. Introduced by Samuel Karelitz, M.D.

This study was designed to determine the effectiveness of phenoxymethyl penicillin in eradicating β-hemolytic streptococci from the pharynx. One hundred sixteen infected patients and carriers from the private practices of three pediatricians and one internist were studied from April, 1956, through May, 1957. Throat cultures were taken from all patients with respiratory illnesses suspected of being caused by β-hemolytic streptococci. The diagnosis of a streptococcal pharyngitis was based upon the findings of β-hemolytic streptococci on throat culture. All patients with an established streptococcal pharyngitis or carrier state received phenoxymethyl penicillin orally, 125 mg. (200,000 units) three times daily for 10 days. The majority (70%) of the patients were 4 to 9 years of age and 9% were over 15 years of age. Among the β-hemolytic streptococci isolated before treatment, 90% were Group A (of which 65% were nontypeable) and 10% were groups B, C, F, G, and nongroupable combined. Follow-up cultures were obtained at least once in 84% of the patients during therapy. Cultures were obtained from all patients after therapy, from approximately 55% of them once weekly for three weeks and once again during the 4th to 8th week of the follow-up period.

The results of treatment with phenoxymethyl penicillin in the 116 patients were cure in 74% and recurrence in 26%. The effectiveness of treatment did not appear to be influenced by age, sex, or

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interval between the onset of illness and the day treatment began. The influence of season, type of case, (acute or carrier state), the presence or absence of tonsils, and the serological characteristics of the microorganism could not be evaluated owing to the paucity of cases.

Among the 30 cases (26%) with bacterial recurrence following treatment, 12 were classified as "relapse," 8 as "reinfections," and 10 as "unknown group and type" of streptococcus. The majority of the bacterial recurrences occurred during the first two weeks after the completion of therapy. Fourteen of the thirty patients with bacterial recurrence also had clinical manifestations of pharyngitis at the time of culture.

The relationship of recurrences to factors in the host, the environment, and the microorganism were studied. Our data indicate that some of the relapses were due to incomplete eradication of the microorganism and inadequate dosage. Among the 30 recurrences, 16 patients received a second course of penicillin; one-half with a standard dose, and one-half with a higher dose (900,000 to 1,000,000 units daily). Compared with the initial cure rate of 74%, the proportion of cures was lower in those retreated with the standard dose of penicillin and higher in those receiving the larger dose. Incomplete serologic data suggest that adequate penicillin treatment of early β-hemolytic streptococcal infections inhibited the development of type-specific antibodies by the host. Among one-fourth of the patients with relapses, household contacts were found to harbor hemolytic streptococci of the same group and type. Thus, even though the organism is eradicated in the host, reexposure to streptococci of the same group and type might result in a relapse.

Complications included catarrhal otitis media in one child two days after treatment and acute glomerulonephritis in another ten days after the end of treatment.

In conclusion, phenoxymethyl penicillin in the dosage used was effective in curing the great majority of β-hemolytic streptococcal infections. A higher cure rate might be achieved in some cases with larger doses of penicillin and in some cases by recognizing and treating household contacts harboring β-hemolytic streptococci. Successful retreatment of recurrent infections may require larger doses than that used for the treatment of the initial infection.

35. Response of Premature Infants to Infection with Certain Common Viruses. HEINZ F. EICHENWALD, M.D.*; HOPE CRAIG PERRY, M.D.,* and OLGA KOCEVALOV, M.D.,* Department of Pediatrics, The New York Hospital—Cornell Medical Center. Introduced by S. Z. Levine.

Before the advent of simplified tissue culture methods, little progress was possible in the study of human viral infection. Especially scant was information concerning the effect of viruses on premature infants where such data might be of particular interest because of their known peculiar response to infection with bacterial agents.

Accordingly, we have attempted to determine the effect on premature infants of a variety of naturally occurring infections with some of the more common viral agents, such as members of the ECHO and adenovirus group. To date, several different viruses have been studied in detail.

The premature infant's clinical manifestations of viral infection often differ sharply from those seen in older infants; for example, agents causing respiratory disease in full-term infants may produce predominantly gastrointestinal manifestations in the immature baby. In general, however, a remarkably high proportion of viral infection remains asymptomatic in premature infants, or only minimal signs and symptoms develop.

Depending on the specific virus and the degree of maturity of the baby, no detectable antibody response to infection may occur, and a prolonged carrier state is produced. On the other hand, infection and viral proliferation may be found in infants with passively acquired homologous antibodies. These and other manifestations of this special host-parasite relationship will be discussed in detail.

36. Hyperlipemia and the Nephrotic Syndrome in Acute Glomerulonephritis. WALTER HEYMANN, M.D., and SYDNEY G. F. WILSON, M.B., M.R.C.P., Ed.,* Department of Pediatrics, Western Reserve University School of Medicine, Cleveland.

During the last ten years serum protein, serum albumin, total lipid, and cholesterol values were obtained from 111 children suffering from acute glomerulonephritis and 108 controls. None of the children with glomerulonephritis are known to have relapsed or developed chronic renal disease. Reexaminations, as long as eight years after onset, were made. Contrary to statements in the literature, hyperlipemia is not infrequently encountered during the acute phase of the disease. Values for serum total lipid and cholesterol above highest normal values (250 and 780 mg. % respectively) were noted in 25% and 35% of the cases respectively. Highest values obtained were 440 mg. % and 2245 mg. % respectively. The hyperlipemia can be noted from 2 to 31 days after onset. Concomitantly, mild, but definite degrees of hypoproteinemia and hypoalbuminemia were also noted. These were found in 47% and 31% of the cases respectively. In these, values lower than 6.3 gm. % for serum protein and 3.8 gm. % for serum albumin were obtained. In addition, some children with acute glomerulonephritis show marked degrees of proteinuria and may

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develop considerable edema and some ascites. A nephrotic syndrome of mild degree and short duration is thus noted in such patients. Ten such cases will be discussed. Because hematuria no longer serves as valuable differential diagnostic symptom, bacteriological studies including nose and throat cultures, ASO titers, and streptococcal group determinations have proved their merit in the differentiation of these cases from the nephrotic syndrome of unknown etiology in infants and children.

37. Pediatrics' Role in Evaluation of Radioactive Fallout Effects on the Population. LEE E. FARR, M.D., Brookhaven National Laboratory, Upton, L. I., N. Y.

The present occurrence of widespread radioactive fallout from weapons testing results in some incorporation of radioactive nuclides in body constituents. In some organ systems these accumulations may have physiological significance. However, to so determine it is required that careful observations be made so that other diseases occurring as the result of other environmental factors or as the result of unknown selective factors in the population will not be confused as to etiology. At the present time natural factors are playing less of a role than ever in health while man-made factors are tending to become predominant. Since the young are susceptible to these environmental changes they present to us a constantly changing yet accurate picture of an integrated result over an appropriate span of years. It is necessary that the pediatrician become fully aware of the important facts in radiobiology that he may accept the responsibility of full child care in these times. A discussion will be developed of some radioactive nuclides and their occurrence in growing organisms.

38. Experimental Infectious Hepatitis: Correlation of Clinical Findings, Liver Function Tests Including Serum Enzymes, and Period of Infectivity. SAUL KRUGMAN, M.D.*; ROBERT WARD, M.D.; JOAN P. GILES, M.D.*; A. MILTON JACOBS, M.D.,* and OSCAR BODANSKY, M.D.,* Department of Pediatrics, New York University, New York.

An attempt to induce "passive-active" immunity to infectious hepatitis (I. H.) was described at the 1957 meeting of this society. During the course of this and subsequent studies 95 patients were fed the Willowbrook strain of I. H. virus. Forty-one members of this group developed clinical or laboratory evidence of infectious hepatitis. These circumstances provided a unique opportunity to study various aspects of infectious hepatitis from its earliest inception. This report is concerned with our observations on the emergence of various manifestations of the disease extending from the period before exposure, through the incubation period and finally during the course of the illness. In addition, studies were performed to determine the period of infectivity of the disease.

Days After I. H. Virus Feeding	Serum Transaminase, Units	Serum Bilirubin, Mg/100 Cc.	Thymol Turbidity, Units	Cephalin Flocculation
—1	40	0.38	1.9	+
5	40	0.45	1.9	+
12	43	0.45	3.6	+
19	34	0.45	2.9	+
26	44	0.45	2.9	+
33	*80*	0.38	2.1	0
35	*899*	0.39	2.1	0
39	*779*	*1.95*	3.8	2+
40 †	*589*	*2.24*	*8.7*	4+
47	*157*	*1.68*	*17.8*	4+
51	69	0.59	*7.3*	4+
54	48	0.59	*8.4*	4+
61	50	0.45	4.4	2+

† Clinical jaundice on the 40th day. Abnormal determinations are italicized.

The following serial liver function tests were correlated with the development of fever, hepatomegaly, and jaundice: serum bilirubin, thymol turbidity, cephalin flocculation, and serum enzymes (phosphohexose isomerase, glutamic oxaloacetic transaminase, and glutamic pyruvic transaminase). Generally, the rise in serum enzymes (1) preceded the appearance of other abnormal liver function tests by 0 to 10 days, and (2) persisted for two to three weeks. The correlation of the serum transaminase with other liver function tests in a patient who acquired infectious hepatitis is shown in the following table.

In general the disease was very mild. Frequently the diagnosis would have been missed without the aid of daily physical examinations and serial liver function tests. Our observations support the impression that many cases of infectious hepatitis in childhood are not recognized.

Hepatitis virus was detected in the stools of patients two to three weeks before onset of illness. This finding suggests that infectious hepatitis has an "alimentary phase" characterized by multiplication and excretion of virus during the incubation period.

39. The Significance of Late Excretion of Tubercle Bacilli in Primary Tuberculosis. EDITH M. LINCOLN, M.D., and AMPARO C. ADIAO, M.D.,* Department of Pediatrics, New York University Medical School, New York.

It is uncommon to find tubercle bacilli in cultures from gastric lavage after primary tuberculosis has

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become retrogressive. Small groups of children have been reported who continued to excrete small numbers of tubercle bacilli six months or more after the first diagnosis of primary tuberculosis. Most investigators interested in this subject agree that late excretion of tubercle bacilli is often associated with abnormalities of the bronchi which are sequelae of primary tuberculosis. Alexander, however, reported recovering tubercle bacilli a year after the initial diagnosis of tuberculous infection in infants most of whom never manifested roentgen or clinical evidence of tuberculosis.

In the Children's Medical Service of Bellevue Hospital in New York, a separate laboratory for microbiologic investigation in the Chest Clinic was established in March, 1947, soon after streptomycin was first used in the tuberculosis ward. From this time until July 1, 1956, 794 tuberculous children were studied. In 290 or 36.5% tubercle bacilli were obtained on culture of gastric fluids obtained by lavage. Excluding children with chronic pulmonary tuberculosis and those who had persistently positive cultures, there were 38 children from whom tubercle bacilli were cultured more than six months after admission. In 31 of these, the cultures had reverted to positive after becoming negative; in 7 all previous cultures had been negative. In 22 patients the positive cultures occurred six months to a year after the initial diagnosis of primary tuberculosis, in 8 patients one to two years after diagnosis, and in another 8 patients two through six years after the first discovery of their tuberculosis. In addition, four patients known to the Chest Clinic between 1930 and 1936 with hearing primary tuberculosis have had tubercle bacilli cultured from gastric lavages 14 to 25 years after the initial diagnosis without any changes in roentgenograms or clinical evidence of tuberculosis.

About one-third of the group had evidence of foci of tuberculosis draining into the upper respiratory tract, tuberculosis of the eye, ear, tonsils, etc.; but except for one patient with a proven primary tuberculosis of the conjunctiva, there was evidence of primary pulmonary tuberculosis as well. Most of the patients had evidence of endobronchial disease, often severe, and there were no patients with negative x-rays.

40. Changes in the Composition of Mucoids of Duodenal Fluid in Cystic Fibrosis of the Pancreas (CFP). ZACHARIAS DISCHE, M.D.*; PAUL A. DI SANT'AGNESE, M.D., and JOSHUA YOULUS, B.S.,* Departments of Biochemistry and Pediatrics, College of Physicians and Surgeons, Columbia University, New York.

Mucoid from one pooled sample of duodenal fluid from patients with CFP (12 cases) and one from control children (11 cases) was fractionated and the composition of all fractions determined (hexoses and fucose by the cysteine-H_2SO_4 reaction; hexosamine by the indole-HCl reaction; sialic acid by its reaction with Ehrlich's reagent). Total mucoid was precipitated by nine parts of a 1:1 mixture of benzene and ethanol, and precipitate was washed and suspended in water. The nonsoluble material present only in patients with CFP (H_2O insoluble fraction=H_2O I. F.) was centrifuged off, and its carbohydrate was extracted by heating for six hours with 10% trichloroacetic acid (TCA) at 90 C. The water soluble mucoid was precipitated with 4% TCA, and the supernatant (80%-90% of total carbohydrate) was fractionated with ethanol.

Four fractions were obtained from fluid of patients with CFP as well as in controls; Fractions A, at 50%, B, at 67%, C, at 90% ethanol, and D, soluble in 90% ethanol. The sialic acid content differed in all fractions and paralleled their solubility in ethanol. In patients with CFP the content in sialic acid of Fractions B, C, and D was significantly increased as compared with controls, whereas Fraction A contained 30%-40% more fucose than Fraction A in controls.

The carbohydrate of the H_2O I. F. in children with CFP did not significantly differ in composition from that of Fraction A. This indicates that the carbohydrate of the former is related to that of the latter fraction. However, the carbohydrate/protein ratio was significantly lower in H_2O I. F. than in Fraction A and about as low as in the nonfractionated total TCA soluble mucoid fraction. The latter was found to consist of a mixture of mucoid and dialyzable protein residue, probably split off from an originally larger mucoid molecule. H_2O I. F. is not solubilized by trypsin. Its loss of solubility may, therefore, partly be due to changes in its protein moiety.

The proportion of the total mucoid of the duodenal fluid in patients with CFP represented by the sum of H_2O I. F. and Fraction A is significantly higher than the proportion represented by Fraction A alone in controls. The proportions of the other three fractions in children with CFP are correspondingly lower. In duodenal fluid of patients with CFP, therefore, there is a significant shift towards the least soluble mucoid fraction. The possible connection between the observed chemical changes in the composition of the duodenal mucoid in CFP and its physicochemical properties and role in the pathogenesis of CFP is discussed.

41. Calcium Excretion During Orthopedic Immobilization in Children. MOLLIE A. COMBES, M.D.,* Department of Pediatrics, The University of Texas Southwestern Medical School, Dallas, Texas. Introduced by Gladys J. Fashena.

Little data is available regarding metabolic changes in the previously active and healthy young

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child undergoing orthopedic surgery and subsequent immobilization. Early operative correction of congenital deformities of bone is increasingly frequent and provides stimulus, material, and demand for assessing calcium, phosphorus, and nitrogen alterations under these circumstances. Reported studies on young adults and adolescents have revealed marked variations in rapidity of onset, severity, duration, and reversibility of hypercalcuria, hypercalcemia, impairment of renal function, and other derangements.

Curiosity regarding what happens in the young child prompted the investigation of urinary calcium, phosphorus, and nitrogen excretion as well as serum values in a 5-year-old white British boy with idiopathic kyphoscoliosis of the thoracic spine during a control period and for five months following anterior thoracic spinal fusion, from the almost complete immobilization in full body plaster through partial mobilization and finally ambulation. During both the ambulatory control interval and the two weeks preoperatively when in plaster alone, urinary calcium excretion remained at 18 mg. per 24 hr. One week following surgery, a five fold increase in urinary calcium excretion to 84 mg. per 24 hr. occurred, followed by return almost to control level at 30 days, after which a second rise began. Subsequently, a second and greater peak excretion to 106 mg. per 24 hr. developed in the ninth postoperative week. This Bactrian pattern of urinary calcium excretion during immobilization has not been described heretofore. Coincidentally, a similar study was carried out in an adolescent white British boy who had contracted suppurative osteomyelitis of the femur at the age of 3 years. Subsequent intervals of prolonged recumbency, with and without surgery and casting, had been attended by the development of calcium-phosphate renal pelvic calculi and hypertension. Full ambulation for the several years prior to this hospitalization was reflected in normal urine and serum values in the control period of the study. Following femoral osteotomy, urinary calcium excretion rose from control levels of 70 mg. per 24 hr. to 182 mg. per 24 hr. at 10 days. The peak, a fourfold increase in calcium excretion to 276 mg. per 24 hr., was reached 30 days postoperatively. During the course of continued immobilization, urinary output of calcium tended to fall in both subjects, still exceeding control values at the time mobilization was instituted. In the 5-year-old, after leg movement was initiated, urinary calcium excretion came down to control levels within five weeks. The downward trend developed more slowly in the adolescent. In both, urinary calcium excretion was found to be below control values after ambulation had been in effect. Serum calcium levels did not change significantly and did not indicate the marked alterations in calcium excretion in the urine. An additional observation was a lack of variation in urine volume accompanying the increased urinary calcium excretion; thus, the concentration of calcium in the urine was markedly raised. Diurnal variation of urinary calcium excretion was followed in other young children in whom it was found that the concentration of calcium in the urine was greatest during the lowest urine volume of the night, a period of complete recumbency for those in casts.

Some implications of these findings with respect to the development of renal calculi and other clinical complications will be discussed.

42. Fate, at Age 2 Years, of Premature Infants Treated with Penicillin and Sulfisoxazole During the First 5 Days of Life. WILLIAM A. SILVERMAN, M.D.,* Department of Pediatrics, Columbia University, New York. Introduced by Rustin McIntosh.

One hundred ninety-two premature infants were enrolled in a controlled neonatal trial to compare the effectiveness of two prophylactic antibacterial regimens (oxytetracycline vs. penicillin/sulfisoxazole). A significant association between penicillin/sulfisoxazole administration and kernicterus was observed among those who died. One hundred six of the infants who participated in this trial left the nursery alive. The fate of these survivors is the subject of the present report.

Sixty-six survivors were available for evaluation at age 2 years. A team of evaluators performed the following examinations: physical, neurological, psychometric, audiometric, speech, dental, ophthalmological, and electroencephalogram. Each evaluator conducted his examination independently and recorded his findings with no knowledge of the neonatal trial conditions and uninfluenced by the judgment of his colleagues.

No meaningful associations were disclosed between the status of the survivors at age 2 and drug administration in the neonatal period.

These examinations afforded an opportunity to explore the associations between other neonatal conditions and status at age 2 years. It was observed that there was no association between the highest bilirubin achieved in the neonatal period (by 32 of the survivors whose daily serum bilirubin had been obtained) and status at age 2 years. Further, no association was noted between status at age 2 and either birthweight, oxygen administration, or respiratory distress in the immediate neonatal period.

More than one quarter of the survivors who were examined exhibited signs that were interpreted to indicate the presence of neurological deficits. There were good correlations between the diagnosis of neurological deficit made by the neurologist and

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the independent diagnoses of mental retardation made by the psychologist, speech retardation made by the speech pathologist, and aplastic dental enamel made by the dentist.

43. Albumin Metabolism in Children with Protein Malnutrition. DAVID GITLIN, M.D.*; JOAQUIN CRAVIOTO, M.D.*; SILVESTRE FRENK, M.D.*; E. L. MONTANO, M.D.*; RAFAEL RAMOS GALVAN, M.D.*; FEDERICO GOMEZ, M.D., and CHARLES A. JANEWAY, M.D., Department of Pediatrics, Harvard Medical School, the Children's Medical Center, Boston, and the Department of Nutrition, Hospital Infantil, Mexico, D. F.

Protein malnutrition, commonly known as kwashiorkor, is still the most prevalent serious metabolic disturbance of children in the world today. Of the biochemical abnormalities associated with this disorder, hypoalbuminemia is undoubtedly one of those found most consistently. Since the metabolic mechanisms operating to produce this derangement are not known, this study was undertaken. Fourteen children with severe protein malnutrition were selected for study. Eleven children exhibited definite edema, but the other three, although malnourished and hypoalbuminemic, had no detectable edema. The children were studied in two periods, each of which was about three weeks in duration, separated by a period of approximately one month. The first study period was begun within 48 hours of admission. All albumin concentrations were determined immunochemically, and I^{131}-labeled human serum albumin was used as the metabolic tracer. After the first study period, the children were placed on therapeutic diets, so that by the time of the second study period, albumin concentrations had reached and were maintained at normal levels; clinical improvement during therapy was marked. By observing the disappearance of radioactive albumin from the plasma after intravenous injection in both study periods, it was determined that hypoalbuminemia in these children with inadequate protein intake was attributable solely to a decreased rate of albumin synthesis.

44. Congenital Bilateral Choanal Atresia in Infancy: Report of Observations on 6 Cases. HARRY MEDOVY, M.D., Department of Pediatrics, University of Manitoba, Winnipeg, Man., Canada.

In November 1951 (*Pediatrics*, vol. 8, no. 5), I reported my experience with five cases of congenital occlusion of the posterior nares, three of them bilateral. The importance of early recognition of this unusual malformation as a possible cause of asphyxial attacks during feeding was stressed. Reference was made to the dependence of the newborn infant on the nasal airway and the spontaneous use of the thumb by one infant as an aid in maintaining an adequate airway.

Three additional cases of bilateral choanal atresia have been observed since the above report was published. The effect of a completely or partially obstructed nasal airway in the infants feeding and breathing habits will be described and the clinical course of these infants reviewed.

45. Mental Development of Children with Blindness Due to Retrolental Fibroplasia. ARTHUR H. PARMALEE JR., M.D.*; CLAUDE E. FISKE, Ph.D.; ROGERS H. WRIGHT, Ph.D.,* and MARGERY G. CUTSFORTH, Ph.D.,* Department of Pediatrics, U. C. L. A. School of Medicine, Department of Psychiatry, U. C. L. A. School of Medicine, and Field Service for Blind Preschool Children, California School for the Blind, Los Angeles. Introduced by John M. Adams, M.D.

Mentally normal blind children can be retarded in their development through neglect, lack of stimulation, and emotional rejection by parents who cannot accept a blind child. These factors may be remedied if recognized. However, some blind children are mentally retarded on an organic basis and cannot be helped beyond their limited potential.

Children who are blind due to retrolental fibroplasia present a special problem in the evaluation of their developmental progress, since they are prematurely born and have suffered oxygen poisoning. These children might be expected to have an increased incidence of mental retardation.

We attempted to determine whether or not there is an increased incidence of mental retardation in children with blindness due to retrolental fibroplasias as compared with children who are blind from other causes. For this study we evaluated the records of 60 school-age children. Thirty-eight had R. L. F.; twenty-two were blind due to other causes. Of the first group, 12, and of the second, 9, were considered mentally retarded. The difference between the two groups was not considered significant. Analysis of the group with blindness due to other causes revealed it to be very heterogeneous. Those diagnosed as having optic atrophy had a high incidence of mental retardation, while some other causes of blindness did not seem to be associated with mental retardation. From this study it would seem that no valid conclusions can be made relative to the significance of prematurity and oxygen poisoning as causes of mental retardation in blind children. The incidence of mental retardation is high in both groups.

Follow up of a previous study of 10 premature infants with blindness due to R. L. F. will be presented. These infants had been selected as probably

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normal on the basis of home observations and were considered normal on testing. One infant was diagnosed at the time of testing as having a severe hearing loss. This group compared favorably with 10 premature infants with normal vision.

It was postulated that these children should continue to do well unless severe emotional problems developed.

It has been possible to retest, at ages 5 to 6 years, 7 of the 10 premature infants with vision using the Stanford-Binet and Vineland tests. All have average intelligence or better.

Nine of the ten children with blindness due to retrolental fibroplasia have been followed by repeated interviews and at least one formal psychological test done after language developed. The interim Hayes-Binet test was used. At present 5 are doing well. The child with hearing loss seems to be mentally normal, although untestable. Two of the children are not doing well, but are not seriously retarded. Efforts to improve the emotional situation in their homes seems to have accelerated their progress. One child is doing very poorly. Biographical sketches of these infants will be presented.

It is our opinion that good developmental progress in the first year of life is a good prognostic sign in blind children, but not infallible.

46. Paralytic Disease with Nonpolio Alimentary Tract Viruses. ALEX J. STEIGMAN, M.D.; MURRAY M. LIPTON, Ph.D.,* and EDWIN RANZENHOFER, M.D.,* Kentucky Child Health Foundation Laboratory of the Department of Pediatrics, University of Louisville.

Ten years ago it was agreed that there are three poliovirus serotypes which may inhabit the human alimentary tract and which are responsible for all cases of paralytic poliomyelitis, as well as for illnesses of lesser severity.

Utilization of suckling mice and of tissue-cultures has more recently uncovered numerous other viral alimentary inhabitants, namely the Coxsackie and the ECHO families of viruses. It was initially believed that these agents were nonpathogenic for the human nervous system and recently these viruses were acknowledged as important causes of the aseptic meningitis syndrome.

We have acquired evidence that member viruses of the Coxsackie (Group A and B) and the ECHO families may alone on occasion produce disease indistinguishable clinically from paralytic poliomyelitis. Their possible importance in relation to disease, to the assessment of poliovirus vaccination, and to related points is unpredictable at this time.

* By invitation.

47. Congenital Mitral Stenosis. ANNA J. HAUCK, M.D.*; ALEXANDER S. NADAS, M.D.*; ABRAHAM M. RUDOLPH, M.D.,* and GEORGE W. B. STARKEY, M.D.,* From the Sharon Cardiovascular Unit of the Children's Medical Center and the Department of Pediatrics, Harvard Medical School, Boston. Introduced by R. Cannon Eley.

Congenital mitral stenosis is a rare anomaly. Prior to 1954, 43 cases had been reported in the literature, and only 8 of these were proven to have no associated lesions.

The purpose of this communication is to present five patients with clinically pure congenital mitral stenosis encountered during the past three years. Clinical observations, physiologic studies, and operative experiences are available on these individuals.

The congenital nature of the malformation was ascertained by the history and operative findings. Symptomatology was characterized by frequent respiratory infections, exertional dyspnea, congestive failure, poor growth, and syncopal episodes. The characteristic physical findings of mitral stenosis were present in four of the five patients. The electrocardiogram showed right ventricular hypertrophy and atrial hypertrophy in every instance. The radiologic examination revealed right ventricular and left atrial enlargement; the pattern of the pulmonary vasculature was nonspecific. At cardiac catheterization, pulmonary arterial hypertension, elevated pulmonary capillary wedge pressure, and relatively normal cardiac output were found.

On account of the marked symptomatology surgical relief of the mitral valve obstruction was attempted in all patients. Three children survived the operation. Postoperative follow-up by means of clinical observations and cardiac catheterization studies showed definite improvement in two and slight improvement in one. The technical difficulties in the operative approach to these valves will be discussed.

48. Studies in Sickle-Cell Anemia: Clinical Management of Sickle-Cell Disease in Infants and Children. ROLAND B. SCOTT, M.D., and ANGELLA D. FERGUSON, M.D.,* Department of Pediatrics, Howard University College of Medicine, and the Pediatric Service of Freedmen's Hospital, Washington.

Sickle-cell anemia (SCA) is a disease of considerable interest to the pediatrician because the disease usually becomes clinically manifest during early childhood. The syndrome can no longer be regarded as a single entity but represents in reality a family of related hemoglobinopathies. The most commonly encountered types are (1) sickle-cell trait, (2) homozygous S sickle-cell anemia, (3) sickle cell-hemoglobin C disease, and (4) sickle cell thalassemia (microdrepanocytosis).

The symptomatology is protean and practically any organ in the body may be involved in SCA. Clinically, the course of the disease may be divided into periods of activity and asymptomatic intervals. In children, crises are often precipitated by or associated with intercurrent respiratory infections and gastroenteric disorders accompanied by vomiting, diarrhea, dehydration, and/or acidosis. Clinically, crises may be classified as (1) "thrombotic," "infarctive," "symptomatic" or "clinical" (localized pain, fever, with no significant change in hemoglobin or other hematologic findings), (2) "aregenerative" or "aplastic" (pain, rapid and severe anemia, decrease in reticulocytes and hypoplastic bone marrow), and (3) "hemolytic" (pain, fever, dramatic fall in hemoglobin concentration, hyperbilirubinemia, and hyperplastic bone marrow).

The management of sickle-cell disease is largely symptomatic and supportive. During a crisis the pathophysiology may consist of any of the following: intravascular sickling, excessive hemolysis of erythrocytes, capillary blockade, increased blood viscosity, infarction, thrombosis, infection, ischemic necrosis, etc. The clinical expression of disease often appears in the form of pain, fever, anorexia, debility, weakness, vomiting, pallor, lymphadenopathy, jaundice, hyposthenuria, leukocytosis, and organ enlargement, particularly involving the heart, spleen, and liver.

In children, sicklemia or sickle-cell trait is practically always asymptomatic and requires no therapy. In our experience, sickle cell-hemoglobin C disease, in the absence of severe osseous involvement (such as aseptic necrosis), is relatively mild and is characterized by mild anemia (compensated), splenomegaly, target cells, and pain during crises. Blood transfusions are rarely necessary; however, intravenous plasma or dextran may be employed with salutary effect for the relief of pain during periods of activity. The crises of homozygous S SCA and sickle cell thalassemia are variable in frequency and severity, but often require positive therapeutic measures. The treatment of these two types will now be considered together.

Over the years, many different agents have been tried by various workers for the control of crises in SCA. We will mention only those with which we have had experience. During "thrombotic crises" and also during periods of quiescence the degree of anemia is characteristically static and blood transfusions are generally not indicated. Packed or sedimented red blood cells are administered in the following situations: 1. severe anemia in hemolytic or aplastic crises (Hgb. less than 5 gm.) where shock is present or imminent; 2. severe complications such as pneumonia, septicemia, etc., where debility is likely to be protracted; 3. in selected cases for elective or emergency surgical operations, and 4. when other medical measures have failed to control crises.

49. Parent Participation in the Hospitalization of Children: A Diagnostic and Therapeutic Aid. ANDREW D. HUNT JR., M.D.,* Hunterdon Medical Center, Flemington, N. J., and Department of Pediatrics, New York University College of Medicine, New York. Introduced by L. Emmett Holt Jr.

The exclusion of parents from hospital wards for children, except during sharply limited visiting hours continues to be widespread pediatric policy. The rationale for continuing this practice appears to be based upon a feeling that parents have an undesirable effect upon their hospitalized children and that effective and efficient diagnosis, therapy, and nursery care depend on an orderly parent-free atmosphere. The turmoil and dislocation of routine which characterize the termination of traditional visiting hours are projected to infinity in the horrified mind's eye of the nurse or pediatrician contemplating the liberalization of visiting privileges.

Considerable literature has appeared calling attention to psychologically deleterious effects of separation of young children from their parents. With a view toward diminishing such unwanted by-products of hospitalization, the opening of a 20-bed pediatric service at Hunterdon Medical Center five years ago provided the opportunity to test the practicability of totally permissive visiting privileges for parents, with cots provided for "rooming in" as desired. In general, the program has been administratively a success, has the indorsement of the nursing staff, and is well received by the public.

Somewhat unexpected has been the contribution to effective diagnosis and therapy provided by this opportunity professionally to observe parents and their children in a controlled setting. Problems such as abdominal pain, anorexia, malnutrition, severe constipation, excessive crying, and the like are frequent causes for hospitalization of children, and in the differential diagnosis of such cases emotional etiology often looms high. The observation of parent-child interaction in the hospital has often been most helpful in clarifying the genesis of such symptoms. Appropriate conferences with parents during the hospitalization made possible by such observations, together, occasionally, with manipulation of visiting hours to provide various degrees of trial separation, become potent therapeutic tools in this setting.

A rather extreme example of this process is that of a 16-month-old girl, admitted in a condition of severe malnutrition, with history and physical examination indistinguishable from those of classical celiac disease. Observation of mother and child in the hospital revealed an intense struggle between them in many aspects of daily living, especially feeding, so that the child's food intake was barely

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life-sustaining. After two weeks, the mother was sent home, and one attendant assumed a carefully supervised mother-substitute role. Shortly, food intake improved, and weight gain was spectacular. Later, the mother was brought back to the ward and her child, and intensively counselled and supported. The result has been a sustained and apparently permanent reversion to normal growth and development.

50. Reaction of Weanling Pigs of Varying Body Composition to Stress. L. S. BAUR, Ph.D.,* and L. J. FILER JR., Ph.D., M.D.,* Columbus, Ohio. Introduced by Warren E. Wheeler, M.D.

Piglets were fed diets to produce varying body fat and water content. They were stressed by deprivation of food and water, and by food deprivation alone.

Domestic farm pigs ingested, *ad libitum* from the third day of life to the 59th day (usual weaning time), either (1) a stock diet containing 25% protein and 2.5% fat or (2) a milk-base food containing 13.8% protein and 26.9% fat (on a dry basis). Pigs so fed were found by chemical analysis to have an average carcass fat content of 15.5% and 34.6%, and carcass water content of 64.0% and 50.4%, respectively.

When five animals so prepared on each diet were subjected to total food and water deprivation, the less-fat animals (Diet 1) survived an average of 28 days; the more-fat animals (Diet 2) survived an average of 21 days. The percentage losses in body stores calculated to have occurred as a result of the stress were as shown in Table 1.

TABLE 1.

	Body Weight	Carcass Water	Carcass Fat	Carcass Nitrogen
Less-fat pigs (Diet 1)	47.3 †	47.3	61.9	35.2
More-fat pigs (Diet 2)	34.8	42.6	30.0	20.3

† Figures are given in per cent.

Serum protein and hematocrit remained relatively constant in both groups throughout the stress. Nonprotein nitrogen rose slowly until 3 to 5 days before death, when there was a steep rise in concentration. Urinary solute concentration rose as high as 2300 mOsm. per liter.

In a second experiment, groups of pigs similarly fed were stressed by food deprivation alone, water supplied *ad libitum*. Under these conditions the less-fat pigs (Diet 1) survived an average of 36 days, the more-fat pigs (Diet 2) an average of 87 days. The latter lost more of their body weight than the less-fat pigs, the values being 55.7% and 40.7%, respectively. Measured indirectly, caloric expenditure of the more-fat animals totaled 57,763 calories (664 per day) in contrast to 29,461 calories (818 per day) for the less-fat pigs. Percentage losses in body contents were calculated as shown in Table 2.

Histopathological examination showed tubular degenerative changes (fat-positive) in the kidneys of the pigs on Diet 2, more pronounced in the pigs deprived of calories only.

Larger stores of body water seemed to lead to longer survival when an animal is stressed by deprivation of calories and water. However, when water is made available, the energy inherent in greater fat stores can be better utilized to prolong life.

TABLE 2.

	Body Weight	Carcass Water	Carcass Fat	Carcass Nitrogen
Less-fat pigs (Diet 1)	40.7 †	28.7	96.5	38.6
More-fat pigs (Diet 2)	55.7	31.5	97.4	42.1

† Figures are given in per cent.

51. Longitudinal Study of Premature and Full-Term Infants: II. Neurological and Intellectual Status at 3 to 5 Years. L. FISCHER, Ph.D.*; W. OPPEL, M.S.*; H. KNOBLOCH, M.D.*; R. RIDER, Sc.D.,* and P. HARPER, M.D., Division of Maternal and Child Health, Johns Hopkins University School of Hygiene and Public Health, Baltimore.

This paper reports some of the findings at the second round of examinations in a long-term study of prematures. At 40 weeks of age, 500 prematures and 492 matched full-term controls were given a Gesell developmental test and a physical examination. The general findings at this age in the neuropsychiatric area indicated that as birth weight decreased the proportion of children with abnormal findings increased.

At 3 to 5 years of age, 900 of the original 992 babies were reexamined using a Stanford-Binet and a modified Gesell examination. These were supplemented by a home interview to obtain an interval medical history, information about physical and social environment and behavior of the child. The findings of the 3 to 5 year examination confirm the 40-week observation, but show a narrowing of the difference between prematures and controls. Numerous differences were observed between the findings at 40 weeks and at 3 to 5 years. These are presented and related to such matters as history of illness and accidents, socioeconomic status, and family characteristics, including interpersonal relationships.

* By invitation.

52. Age of Attaining Bladder Control. W. Oppel, M.S.*; R. Rider, Sc.D.*; L. Fischer, Ph.D.*; H. Knobloch, M.D.,* and P. Harper, M.D., Division of Maternal and Child Health, Johns Hopkins University School of Hygiene and Public Health, Baltimore.

The age of developing day and night bladder control by 900 children from 3 to 5 years of age was obtained from the mother by interview at home. One half of these children were prematures, half were matched full-term controls; all have been followed since birth, and their parents have been accustomed to our routine of interval history and examination. The questions about sphincter control were placed in the middle of a long interview which asked many questions of a social and personal nature.

A life-table method of analysis allows one to plot the development of sphincter control as a function of age. The curve thus obtained shows that less than 70% of these children developed complete bladder control by 4 to 4½ years; another 10% to 15% wet less than once a week. These data indicate a slower rate of development of bladder control than that given by most published estimates.

The findings will be related to length of gestation, to sex, race, socioeconomic status, to developmental and intelligence scores, and to other data. Evidence is available that the control children are reasonably representative of children of this age in Baltimore. The implications of these findings for advice to parents will be discussed.

53. Measurement of "Trapping" of Air in Intrapulmonary Gas Distribution. George R. De Muth, M.D.*; David G. Dickinson, M.D.,* and James L. Wilson, M.D., Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, Mich.

A test based upon changes in the calculated lung volume during equilibration with oxygen has been adapted and utilized for an assessment of abnormal intrapulmonary gas mixing and trapping. It requires but two minutes cooperation from the patient and offers us a sensitive measurement, easier to perform than the usual indices (N_2 elimination, physiological dead space, etc.).

The technique involves continuous measurement of the inspired and expired nitrogen concentrations (with a Lilly analyzer) while the subject rebreathes into a bag of oxygen for two minutes. At any point the equilibrating lung volume can be calculated by this formula: $V_{Lung} = \frac{V_{bag} \times F_{N\ bag}}{0.80 - F_{N\ end\text{-}tidal}}$

Because of the method, the values so calculated will inevitably change. After an initial period the values rise steadily in a straight line the slope of which represents the volume of air (nitrogen) "added" to the equilibrating volume per minute. The "addition" is derived from two sources; one, nitrogen released from tissue and blood, and two, that released from poorly communicating and poorly equilibrated lung spaces (trapped air). Correction for the first can be made and the volume of the second thus obtained. This can then be adjusted for body size or predicted lung volumes.

In practice, the control subjects have shown quite constant and low values. Patients with a variety of lung diseases have shown from small to large increases which vary with the particular disease and its status. These results and examples of the use of the test for assessment and therapy evaluation will be given.

54. The Effectiveness of Oral Penicillin Prophylaxis of Rheumatic Fever: A Review of 10 Years Experience in a State Program. Ruth Whittemore, M.D.,* Department of Pediatrics, Yale University School of Medicine, New Haven, Conn. Introduced by Nelson K. Ordway.

This report presents the development over the past 10 years and the present status of the Connecticut program for the prevention of rheumatic fever recurrences. Practical facts concerning the efficacy of oral penicillin as a prophylactic agent, some tentative conclusions as to appropriate dosage, and better understanding of many factors which influence patient participation in the program have become apparent.

Although this prophylactic program was first available only through the pediatric cardiac clinics at Yale, it has recently expanded to include over 4000 patients throughout the state (about 50% children) upon application from their physician to the Connecticut Heart Association. The New Haven clinics still serve the largest single group of patients.

When oral penicillin tablets first became available, 150,000 units of buffered penicillin G were given daily in divided doses, but β-hemolytic streptococci were present in 10% of nose and throat cultures obtained at regular intervals both before and after prophylaxis was commenced. The dose was, therefore, increased to 300,000 units per day in divided doses with resultant marked reduction in the percentage of positive cultures. Since the inception of the Connecticut Heart Association program three years ago, a single daily dose of 250,000 units of buffered penicillin G has been given to conform with the American Heart Association recommendations at that time.

From the first it has been realized that the importance of faithful participation has had to be repeatedly emphasized to the child and his family. Clinic personnel have reviewed the need for peni-

* By invitation.

cillin on each visit and, in addition, public health nurses have been asked to remind these patients in the school. Despite these efforts, a large proportion of patients have failed to take their penicillin each day.

In the New Haven clinic, factors influencing patient participation have been studied with particular reference to two groups of children. In the first group, a study of family influence in the children under 12 years of age from 80 families was carried out by a medical sociologist unrelated to the cardiac clinic. Fifty-five percent of these patients satisfactorily took their penicillin. The degree of patient participation could be correlated both with the mother's understanding of the need for penicillin and with her concept of the clinic personnel's opinion of her (her "reflexive self concept"). In the second group, members of the adolescent clinic, the desire to gain independence as well as problems of family influence led to even poorer participation, approximately 30%.

At the present writing, recurrences in the state have been reported in 1% of patients, two-thirds of these being in children. In the New Haven clinic group, however, the over-all recurrence rate is approximately 3%; significantly, those not faithful in taking penicillin had approximately 6% recurrences in comparison to the faithful participants, who had less than 1%. Investigation of the bona fide break-throughs, even though small in number, together with the apparent benefits from multiple dosages observed in the earlier phase of the program, leads to the consideration that oral prophylactic penicillin should be administered in daily divided doses.

55. The Definition of Hemolytic Disease Due to Anti-A or Anti-B. HAROLD H. GUNSON, M.B., Ch.B.,* The Rh Laboratory, Department of Pediatrics, University of Manitoba, Winnipeg, Man., Canada. Introduced by Bruce Chown.

In 1957 I reported three cases which I considered to be hemolytic disease of the newborn due to the combined action of anti-A and anti-Rh. In the current issue of the *Year Book of Pediatrics*, Diamond has questioned whether such a diagnosis was justified, doubting that the presence of anti-A in the serum of a newborn Group A infant proves that this infant has hemolytic disease of the newborn. He considers this "a presumption . . . proper for speculation." I have attempted to investigate this question.

Among 67 Group A or B infants born to Group O mothers, homologous antibody was present in the sera of 14 and absent in 53. The cells of all 14 infants were direct Coombs positive. From 13, homologous antibody was eluted from the baby's cells. The reticulocyte counts and the serum bilirubin levels were on the average higher than in the remaining infants. Eight became jaundiced within 24 hours of birth.

One has necessarily to be critical of the definition of hemolytic disease due to anti-A or anti-B, since the degree of clinical disease is extremely variable. Many subclinical cases with serological evidence of cell sensitization to anti-A or anti-B have to be recognized. The evidence from the above series supports the diagnosis of mild hemolytic disease in those infants who had free homologous anti-A or anti-B in their cord blood.

56. Use of Surveys and Seminars as Instruments in Improving Pediatric Education. MYRON E. WEGMAN, M.D., and JAMES G. HUGHES, M.D., From the Pan American Sanitary Bureau, Regional Office for the Americas of the World Health Organization, Washington.

Surveys of pediatric education, similar to those in the U. S. A., Canada, Australia, and New Zealand, have recently been carried out in 18 countries of Europe and in 19 countries of Latin America, plus Jamaica and Surinam. The recent surveys were based on questionnaires to each school supplemented by personal visits to selected schools.

In the survey in the Americas, all 79 medical schools provided information. Great variation was apparent in size of class in the year pediatrics was taught, from 720 to 6 students. Ten percent of the schools had 47% of the students, while 50% of the schools had 13% of the students. Excessive student bodies were related to unselected admissions; resources in faculty and facilities were frequently disregarded. Total hours of instruction received by the individual student varied from over 400 to 72 with a median of 225 hours. Departments with more total hours devoted a much higher proportion of the time to practical work. In 16 departments, no individual work was reported with patients in hospital or outpatient department. In an additional 11, only hospital experience was provided. Proportion of pediatric hours to total hours of instruction in the entire medical curriculum of six to seven years, varied from 6.9% to 1.5%. Schools with percentages over 5 generally had over 300 hours in pediatrics. In general adequate clinical material was available, although four departments, with 820 students, reported no hospital beds at all.

More than 50% of faculty members devoted less than one-quarter of their time to teaching activities. Two schools had full time teachers in pediatrics. Ratio of teaching hours to students, dividing total faculty hours by number of students, varied from 224 to 1. Definition of "cátedra" or "chair" varied from country to country; often clinical pediatrics of older infants and children was separated from puericulture, usually confined to growth and devel-

* By invitation.

opment, child hygiene, and diseases of infancy. Laboratory procedures were included as a student exercise in less than half the departments. Many schools did no teaching on child health services, crippled children, or psychologic and psychiatric problems. Very little use was made of child health centers or school health services.

Results of the various surveys supplied important background for the World Health Organization's Study Group on Pediatric Education in Stockholm in 1956. The stimuli of the survey itself and analysis of the results have resulted in serious self-examination and improvement in many schools. Preliminary results were used as basis for a two-day Round Table on Pediatric Education for medical schools of Central America and Panama at the Central American Pediatric Congress, Gautemala, 1956. The data have also been used in preparing both national and intercountry seminars on pediatric education.

It is believed that the simplified questionnaire, followed by group meetings to analyze results in the light of established standards of pediatric education, constitutes a simple technique which is producing positive results in improvement of pediatric education.

57. Salmonellosis in a Premature Nursery Unacompanied by Diarrheal Disease. JAMES WATT, M.D.*; MYRON E. WEGMAN, M.D.; O. WHARTON BROWN, M.D.*; D. J. SCHLIESSMANN, M.S.*; ELIZABETH MAUPIN, B.S.,* and EMMARIE C. HEMPHILL, M.P.H.,* The Diarrheal Disease Investigations Unit, U. S. Public Health Service, and the Louisiana State University, School of Medicine.

Six infants who later turned out to be infected with Salmonella tennessee were admitted simultaneously to a large premature nursery. At the time of introduction of the infected infants, a long term study of enteric bacteriology was under way in the nursery with a regular schedule of cultures on all infants. Subsequent spread of the infection within the nursery provided an unusual opportunity to trace the epidemiology of a Salmonella infection within a determined environment.

Careful evaluation of all pertinent signs and symptoms failed to reveal evidence of illness among any infected infants. A few infants were treated with antibiotics which failed to eliminate the infection. The epidemic subsided spontaneously after four months. The infected group did not differ in race, sex, or weight distribution from the entire nursery population during the period of the epidemic. Among infants infected in the premature unit, age at infection was appreciably greater for infants under 1500 gm. as compared with those over 1500 gm.

Original source of the infection could not be determined. The epidemic spread occurred in two groupings. Five new cases appeared during the three weeks immediately after admission of the original cases. After three weeks of no new cases, a second outbreak developed, involving 21 infants over a four-week period. Two further sporadic cases occurred subsequently.

No evidence of mass contamination of food or water could be demonstrated. It was possible to demonstrate occasional positive cultures from cribs or units of known positive infants and on a few occasions organisms were found on communal equipment. Salmonella tennessee was recovered once from the air, once from an air-conditioning filter, and once from the hands of a member of the nursery personnel. Rectal swabs of nursery personnel were uniformly negative.

A study of workload and nursing supervisory statistics indicated correlation of increased spread with decreased nursing care. On the basis of epidemiologic analysis it is inferred that defective nursing techniques, particularly hand washing, constituted the chief mode of spread.

58. Further Studies on Antibody Responses and Their Persistence in Infants Given Poliomyelitis Vaccine. RANDOLPH BATSON, M.D.*; AMOS CHRISTIE, M.D., and DOROTHY TURNER, M.D.,* Department of Pediatrics, Vanderbilt University, School of Medicine, Nashville, Tenn.

Three years ago a study was initiated to determine the degree and persistence of the young infant's immunologic response to poliomyelitis vaccine given separately and combined with other antigens. The preliminary report was presented to this society last year. It was concluded that infants as young as 6 weeks could be successfully immunized with poliomyelitis vaccine given separately and mixed in the same syringe with other vaccines. This combination produced no adverse reactions and did not interfere with the development of antibodies to diphtheria and pertussis. There was no apparent interference in antibody responses by the presence of maternal antibodies.

The study of these two groups of infants has continued and antibody collections have been made on 57 of these infants one year after the third polio vaccine injection. These data will be presented and lead to the conclusion that, although 4 months after the third injection antibody levels were quite high, at 12 months there was a definite and striking decrease in antibody titers. This decrease occurred in both groups of infants, namely, those receiving poliomyelitis vaccine given separately and those receiving poliomyelitis vaccine combined with other antigens. Because of this we suggest that serious consideration be given to the routine administration of a fourth injection of

* By invitation.

1 cc. of poliomyelitis vaccine 12 to 18 months after the third injection. At least this practice would seem advisable unless it can be demonstrated that the state and degree of hypersensitivity without detected antibodies is sufficiently great to result in a protective response when natural infection occurs.

In addition to the above, information will be available in regard to other study groups: Group 3 consists of infants given their first injection at one day of life, the second at 6 weeks of age, and the third at 8½ months of age; in Group 4, the mothers received 1 cc. of poliomyelitis vaccine four to six weeks prior to the expected date of confinement, their infants received the second injection at one day of life, and the third injection at 7 months of age. These studies may have little practical application to vaccine administration but may help to clarify the question of possible interference in the infants antibody response by passively transferred maternal antibodies.

A study is underway to determine the advisability of giving the third poliomyelitis vaccine injection 2, 3, 4, or 5 months after the second injection. It is possible that enough data will have been collected to be of statistical significance.

59. An Evaluation of Current Pediatric Practices in Oxygen Therapy. RANDOLPH BATSON, M.D.,* Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tenn. Introduced by Amos Christie, M.D.

Oxygen tents and many other commonly used methods for delivering oxygen have not proven satisfactory for the management of sick hypoxic children. After this inadequacy was demonstrated by measurements of oxygen concentration, humidity, and temperature, other methods for therapy were examined. Earlier observations by Burgess and Burgess on the use of an open-top oxygen box led us to believe that by utilizing modern materials and nebulization techniques an even better oxygen compartment could be made. Such a device was constructed and is now used almost exclusively in Vanderbilt University Hospital as the preferred method for administering oxygen and providing high humidity to infants and small children. The experience with this technique has extended over a period of 15 years during which time the oxygen box technique has been used in over 15,000 treatment days.

Extensive data demonstrates satisfactory control over temperature, carbon dioxide excess, and humidity, as well as oxygen content, e. g., an oxygen flow rate of 5 liters per minute into such an oxygen box would be expected to produce the following approximated values in the atmosphere surrounding the patient; oxygen concentration of 60 volumes per cent; relative humidity of 70% or greater depending upon the need; temperature of 60 F and carbon dioxide content of less than 0.2%. Comparisons are made between this and other methods for delivering oxygen. Numerous measurements of oxygen content, temperature, and humidity have been made under varying conditions; these related to oxygen flow rates, atmospheric conditions in the patient's room, atmospheric characteristics at various levels within the compartment, effects of temperature changes within the compartment, and the reactions of patients to these variables.

Conclusions from these observations are as follows.

1. An oxygen flow rate of 4 liters per minute in an open-top oxygen box results in greater oxygen concentration than can be obtained in oxygen tents with flow rates of 10 to 15 liters per minute.

2. Therapeutic oxygen content can be obtained rapidly (within 10 minutes).

3. Relative humidity and temperature range are satisfactorily controlled.

4. Therapeutic oxygen concentrations are maintained during patient care procedures. Patients may be given formulas, injections, or oral medications without reducing oxygen content below therapeutic levels.

5. Patients may be closely observed through walls of transparent plastic material.

6. Construction is such that the materials are durable and the walls are stable.

7. Patients do not experience claustrophobia.

8. There is adequate mechanical wash-out of carbon dioxide.

9. Family and medical personnel may converse with the patient in normal tones.

10. Extremely high humidity or "mist" can be readily produced for the treatment of respiratory infections.

11. Operation of the device incurs less than half the expense of operating oxygen tents, and the initial cost of equipment is far less.

12. The device can be constructed in most machine or equipment shops.

60. The Mechanism and Clinical Significance of an Abnormality in Glutathione Metabolism of Erythrocytes from Normal Newborns. W. H. ZINKHAM, M.D.,* Department of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore. Introduced by Robert E. Cooke.

Three biochemical abnormalities have been described in erythrocytes from patients with certain drug-induced hemolytic anemias: a low whole blood reduced glutathione (GSH), a marked decrease

* By invitation.

in GSH after incubation of blood with acetylphenylhydrazine (GSH stability test), and a deficiency of glucose-6-phosphate dehydrogenase activity (G-6-P D). These defects are genetically determined, are transmitted by a sex-linked gene of intermediate dominance, and have been observed in four groups: Negro, Greek, Jew, and Italian.

An alteration in GSH metabolism has also been demonstrated in red cells from the majority of normal newborns, both Negro and white. Although whole blood GSH values are similar to or higher that those observed in normal adults, the GSH stability test is abnormal. This phenomenon is transitory, and in a series of 66 newborns, 1 to 84 hours old, values for the GSH stability test were approaching normal between 36 and 84 hours of age. In 13 of these babies, simultaneous GSH determinations and assays for G-6-P D activity were done. Values for enzyme activity were higher than those observed in normal adults, suggesting that the mechanism for GSH instability differs from that observed in red cells from patients with drug-induced hemolytic anemias.

Since the metabolic pathways for maintaining a normal level of erythrocyte GSH are closely related to the availability and utilization of glucose, the effect of added glucose on the GSH stability test was studied. In a group of 33 newborns, 1 to 55 hours old, the per cent decrease of GSH after incubating blood with acetylphenylhydrazine varied between 40.4 and 88.3. After the addition of glucose in a final concentration of 30 to 160 mg. %, the range was 17.7% to 24.6%. Glucose protection was most marked in 10 infants under 12 hours of age (88.3% decrease before and 21.0% decrease after the addition of glucose). The oxidation of GSH by APH or vitamin K could be reversed by adding glucose, suggesting that these compounds did not alter the activity of enzymes or co-factors essential for reducing glutathione. Preliminary studies indicate that the inadequate supply of glucose for the in vitro GSH stability test is secondary to a low level of blood glucose as well as an increased rate of glucose utilization by newborn blood.

In four Negro male infants with a deficiency of erythrocyte G-6-P D activity, final concentrations of 160 to 1600 mg. % glucose had no effect on the markedly abnormal GSH stability test. The mothers of these infants had a partial to complete deficiency of G-6-P D, indicating a genetic background for the metabolic defect in the red cells of their offspring.

Thus the marked in vitro instability of GSH in newborn red cells may be associated with at least two defects: one, a deficiency of substrate, glucose, and the other, a deficiency of enzyme, G-6-P D. The amount of glucose necessary to protect GSH under the conditions of the in vitro GSH stability test is so small that only in unusual circumstances would hypoglycemia contribute to the evolution of chemically induced hemolytic anemias. Certainly in the case of newborns with decreased erythrocyte G-6-P D activity, even super-normal amounts of glucose will probably have little effect on the severity of hemolysis.

61. Cerebrospinal Fluid Levels of Glutamic Oxalacetic Transaminase and Lactic Dehydrogenase in Normal Newborn Infants. MIRIAM LENDING, M.D.,* Department of Pediatrics, New York Medical College, Flower and Fifth Avenue Hospitals, New York. Introduced by Lawrence B. Slobody.

There have been no reports to our knowledge on the cerebrospinal fluid (CSF) levels of glutamic oxalacetic transaminase (GOT) and lactic dehydrogenase (LDH) in newborn infants. We have been studying these values in normal newborns and in those with intracranial pathology. The levels in 52 normal newborn infants ranging in age from 2½ to 240 hrs. are reported here.

These infants were the products of uneventual gestations and deliveries and appeared normal under continued observations. CSF was obtained by lumbar puncture and plasma from femoral venipuncture was drawn simultaneously. GOT and LDH levels were measured using the methods of Karmen et al. for GOT and Wroblewski and LaDue for LDH. Only a single lumbar puncture was done on any individual infant and each specimen of CSF was centrifuged and separated immediately.

The results obtained are shown in the Table.

There was no significant difference noted in the levels at the different ages from 2½ to 240 hrs. The CSF levels of GOT in the newborn infant are apparently lower than those reported in normal adults. These CSF levels were higher in the male than in the female infant as has also been noted in normal human adults. The plasma GOT con-

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GOT in CSF and Plasma, Units/Ml/Min.

	Newborns, No.	Range	Av.
CSF	52	1.0-10.0	4.7
Plasma	52	5.0-102	37.1

LDH in CSF and Plasma, Units/Ml/Min.

	Newborns, No.	Range	Av.
CSF	52	3.3-120	32.7
Plasma	52	370-2,340	1,175.0

centrations in these normal newborn infants is similar to those previously reported by Kove and his associates.

62. Experimental Glomerulonephritis Produced by Transfusion of Serum from Nephritic Rabbits. KURT LANGE, M.D.*; EUGENE J. WENK, M.A.*; JEROME NOBLE, M.D.,* and EDWARD WASSERMAN, M.D.,* Departments of Pediatrics and Medicine, New York Medical College, Flower and Fifth Avenue Hospitals, New York. Introduced by Lawrence B. Slobody.

The transfusion of serum from rabbits with acute glomerulonephritis produced by anti-rabbit-kidney duck serum did not cause nephritis in six normal rabbits. When 10 rabbits were sensitized with anti-rabbit-kidney duck serum. (ARbKDS), however, and shortly thereafter transfused with serum of rabbits that had acute glomerulonephritis, disease occurred without delay and showed the typical morphologic and clinical characteristics of acute glomerulonephritis. The γ-globulin fraction of the ARbKDS as well as the γ-globulin fraction of serum of nephritic rabbits produced results identical with those of the ARbKDS and the serum of nephritic rabbits. When either serum or γ-globulin of rabbits previously immunized against unmodified duck serum was transfused into 12 sensitized rabbits, the anticipated delay period was not shortened.

After the injection of 10 cc. of ARbKDS both acute glomerulonephritis and high titers against duck serum will occur after an interval of five days. When, however, 2 cc. of ARbKDS and 8 cc. of unmodified duck serum were used as the immunizing material, the high titer against duck serum was again observed on the fifth day, but the appearance of the disease was delayed until the eighth day. This eight day interval is identical to what is seen after the injection of 2 cc. of ARbKDS only. Similarly, in animals previously sensitized with duck serum, the injection of ARbKDS produced a rapid anamnestic reaction to normal duck serum proteins, as evidenced by the appearance of high antiduck serum titers within 48 hours. These high titers again were not immediately accompanied by disease. Glomerulonephritis occurred after the usual five day interval, indicating that the high antiduck serum titer in no way influenced the appearance of the disease.

Thus, it would appear that the antibody which produces experimental glomerulonephritis is not directed against normal duck serum proteins but against the localizing fraction therein.

63. Paper Electrophoretic Study of Cerebrospinal Fluid Proteins in the Normal Newborn Infant. M. LENDING, M.D.*; S. J. PILIERO, Ph.D.,* and C. MAHAIRAS, M.S.,* Departments of Pediatrics and Anatomy, New York Medical College, Flower and Fifth Avenue Hospitals, New York. Introduced by Lawrence B. Slobody.

The present study was undertaken to establish values for the distribution of proteins in cerebrospinal fluid in normal newborn infants. Cerebrospinal fluid was obtained by lumbar puncture from 25 normal newborn infants ranging in age from 2½ to 114 hours.

Paper electrophoresis requires a 2% to 5% protein solution, which necessitates the concentration of the cerebrospinal fluids. It was possible to obtain the necessary concentration utilizing only 3 ml. aliquots of cerebrospinal fluid with the dialyzing technique of Grogan and Roboz (1955). Paper electrophoresis was performed with a Spinco hanging-strip electrophoretic apparatus. Eight strips of Whatman 3 mm. filter paper were run simultaneously. Veronal buffer at pH 8.6 and 0.05 ionic strength was used. After initial equilibration, cerebrospinal fluids in 100λ amounts were applied at the apex of the wet strips. A constant current of 6.9 ma. was employed for 16 hr. runs. After drying at 90-120 C for 30 minutes, duplicate strips were stained with Amidoschwarz 10B dye solution for the protein pattern. Densitometry was performed with a Spinco servotype integrating scanner.

The cerebrospinal fluid proteins occurred as five bands with their corresponding paper strips in the order of increasing mobility to γ, β, α-2 and α-1 globulins and albumin. In addition to the proteins present, the prealbumin or X fraction which moves faster than albumin was detected at very low levels and is not included along with the protein percentages. The values for the protein components of cerebrospinal fluid in 25 normal newborn infants are given in the Table.

The previously reported studies on cerebrospinal fluid proteins have concerned adults, older children, and abnormal infants of varying ages. Studies are

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	A/G Ratio	Albumin %	α-1 Globulin %	α-2 Globulin %	β-Globulin %	γ-Globulin %
Mean	0.75	42.2	6.6	6.9	17.4	26.9
Standard error	±0.04	±1.34	±0.30	±2.3	±1.3	±1.1

in progress on the relationship between the concentrations and distribution of proteins in serum and cerebrospinal fluid in the normal and diseased newborn infant.

64. A Comparative Study of 26 Sets of Multiple Births. LOREN MCKINNEY, M.D.*; DONAL DUNPHY, M.D.,* and VIVIAN PESSIN,* Department of Pediatrics, University of Pittsburgh School of Medicine and Children's Hospital, University of Buffalo School of Medicine and Children's Hospital, Buffalo. Introduced by Mitchell I. Rubin.

A comparative study of 25 sets of twins and 1 group of triplets was made, in an attempt to ascertain whether any physiological advantage or handicap resulted from the order of birth. Comparison between the first and second born includes detailed observations concerning delivery, birth weight, and cord blood gas analysis. Evidence will be presented indicating that there is no biological difference between the first and second born with respect to cord blood vein oxygen content or saturation, pH, pCO_2, or CO_2 content. The differences which have been found indicate that there is a tendency for the second twin to have a lower oxygen capacity and a higher birth weight. The results of this study suggests that there is no physiological basis for considering the first or second born twin as being in a more advantageous position at least in so far as these various factors are concerned.

The results of psychometric testing indicates that there is no association between the order of birth and subsequent test scores obtained on either the Cattell Infant Intelligence scale or the Stanford-Binet Intelligence test at 4 or 5 years of age. Evidence will be presented, however, indicating that twins as a group achieve lower test scores at 6 months of age and again at 4 or 5 years of age compared with nontwins. These lower test scores are not related to the degree of prematurity of the infants as manifested by birth weight.

65. Immunization with Orally Administered Attenuated Live-Virus Poliomyelitis Vaccine. MAURICIO MARTINS DA SILVA, M.D.*; JOHN L. MCKELVEY, M.D.*; KONALD A. PREM, M.D.*; EUGENE A. JOHNSON, Ph.D.,* and HERALD R. COX, Sc.D.,* Departments of Obstetrics, Pediatrics, and the School of Public Health, University of Minnesota, The State Health Department, and the Viral and Rickettsial Research Division, American Cyanamid Company. Introduced by John A. Anderson.

The attenuated live-virus poliomyelitis vaccines administered orally in this study were prepared from the SM strain of Type 1, the MEF_1 strain of Type 2, and the Fox strain of Type 3 viruses. The vaccines were given orally to 25 infants under the age of 6 months, born of mothers vaccinated during pregnancy with Salk vaccine. Type 1, 3, and 2 vaccines were given separately, in succession, and at intervals of not less than 3 weeks.

The fate of the viruses and the immune response in the orally vaccinated child and in all members of the family unit was followed by serial stool cultures and serial serum antibody determinations. The stools of all subjects were examined for virus previous to the administration of the first oral dose and at weekly intervals thereafter for 5 to 12 weeks. The antibody titers for all three types of viruses were determined on all subjects before virus feeding and at approximately 3-month intervals thereafter up to one year. The biological characteristics of the viruses recovered from the stools of vaccinated infants and from the familial contacts was evaluated and compared with the original attenuated live-virus poliomyelitis vaccine.

The antibody responses to the orally fed attenuated viruses was satisfactory for Types 1 and 3, but poor for Type 2. When compared with infants inoculated with Salk vaccine, the responses were as good and often better. Satisfactory antibody responses were found in other members of the family demonstrating the presence of viruses in their stools. Antibody responses against Types 1 and 3 viruses were also occasionally demonstrated in familial contacts failing to have viruses in their stools.

Following feeding of the oral vaccines to the infants, virus could be recovered in the stools in 72%, 4%, and 44% for Types 1, 2, and 3, respectively. Virus was present in the stools of vaccinated infants for as long as seven weeks after oral vaccination. Evidence of spread to other members of the family was determined by the isolation of virus from their stools or by a significant antibody rise against all three types of virus. The incidence of secondary infections in the family constellation was (excluding the father) for Type 1, 68%, for Type 2, 16%, and for Type 3, 60%. Virus was found in the stool of contact infections for as long as five weeks.

The biological characteristics of Types 1 and 3 attenuated viruses recovered from the stools of vaccinated infants were compared with the original oral vaccine. Intracerebral inoculation in monkeys of a 10% stool suspension obtained from the vaccinated and their contacts demonstrated slight increase in paralytogenic activity. The Type 3 virus, on the other hand, failed to demonstrate increased paralytogenic activity.

No significant untoward reactions were observed in the infant or in the members of their families attributable to the vaccine. Seventeen infants, fourteen mothers, and nine siblings excreted large amounts of Type 1 virus over an extended period of time. No contact cases of paralytic poliomyelitis

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were observed despite the fact that many of these families live in crowded housing situations highly favorable for intra- and extrafamily spread. This study indicates that orally administered attenuated live-virus poliomyelitis vaccine produces a satisfactory antibody response in infants and in familial contacts. This study has been extended and at present 152 families representing 600 subjects are being immunized with all three strains of the attenuated viruses.

65. Male Pseudohermaphroditism in 3 Siblings. CHARLES H. BAUER, M.D.*; MYRON WINICK, M.D.*; LEWIS ARNOW, M.D.*; DONALD P. BEIRNE, M.D.,* and NORMAN KRETCHMER, M.D., Ph.D.,* Department of Pediatrics, The New York Hospital-Cornell Medical Center, New York. Introduced by S. Z. Levine.

This is a report of three siblings, 13¾ years, 12¾ years, and 3 months of age, with male pseudohermaphroditism, who were all raised as females. Familial male pseudohermaphroditism is uncommon, and early diagnosis is exceedingly important for psychological adjustment.

The two older children have a number of features in common. Each is tall for her age, and has large hands and feet, an enlarged clitoris, normal appearing labial folds, and a female type of introitus with the urethral opening at the base of the clitoris. Bone age, urinary 17-ketosteroids, and serum electrolytes were normal. Buccal smears showed a male chromosomal pattern.

The oldest sister has a vagina with no palpable cervix, uterus, or adnexa. Two small masses were present in the inguinal region. The second sister has no evidence of vagina or any internal female organs. A left inguinal mass and right inguinal hernia scar was noted in this child.

Laparotomy revealed no evidence of any female organs in either of the two older sisters. Clitorectomy was performed in both children, bilateral orchiectomy in the older sibling, and excision of the left inguinal mass in the second sister. Pathological examination indicated that the inguinal masses were hypoplastic testes without the presence of spermatogenesis.

The youngest sibling has enlarged labia majora resembling a bifid scrotum, a normal-sized clitoris, an urethral opening just below the clitoris, bilateral labial masses 1 cm. in diameter, and buccal smears which show a male chromosomal pattern.

Problems of correct diagnosis, sex determination, management, and familial incidence of the disorder will be emphasized in this discussion.

* By invitation.

67. Obligatory Renal Water Requirements in Infants Fed Varying Formulae: Prematures, Newborns, and Infants with Water Deprivation and Diarrhea. PHILIP L. CALCAGNO, M.D.*; P. K. MUKHERJI, M.D.,* and MITCHELL I. RUBIN, M.D., University of Buffalo School of Medicine, Department of Pediatrics, and the Children's Hospital of Buffalo, Buffalo, N. Y.

With the increasing tendency to feed concentrated milk formulae to newborn infants, it is important, because of the lowered capacity of the kidney in the newborn period to excrete solutes, to consider the solute content of the formula. Hyperosmolarity and severe hypernatremia with diarrhea in infants is a common clinical experience, which also emphasizes the need of an understanding of osmolar excretion.

Forty-five normal newborn infants, twelve premature infants, ten infants with diarrhea, and five infants who were water-deprived were studied with regard to water, osmolar, electrolyte, and nitrogen excretions while on various formulae. The following formulae were used because of their varying osmolar contents: 1. colostrum; 2. human breast milk; 3. simulated human breast milk; 4. dilute evaporated milk formula (1:2 dilution) with added carbohydrate; 5. whole cow's milk, and 6. protein milk.

Twenty-four hour urine collections were made on the third, fourth, and fifth days of life of the newborn infants, and 48 hour collections were obtained on the other infants in this study. Daily milk samples fed these infants were analyzed for osmolar, nitrogen, and electrolyte content.

The results in the newborn infants show the "low solute milk" formulae presented 10 to 14 mOsm. for renal excretion each day while the "higher osmolar" formulae averaged 27 mOsm. Calculated renal water in excess of obligatory expenditure was in the higher osmolar load formulae approximately one half that observed in the lower osmolar load formulae.

In the group of 12 premature infants studied, the renal osmolar excretion for the higher osmolar diets was 16.1 mOsm. per kilogram body weight per day, while on the lower osmolar diets, the renal osmolar excretion was 8.7 mOsm. per kilogram body weight per day. The renal water in excess of obligatory expenditures was 25% greater in the infants fed the lower osmolar milk when compared with those given the higher osmolar milk formulae.

In the 10 infants recovering from diarrhea who were studied when oral feedings were resumed, the infants on the lower osmolar formulae excreted an average of 13 mOsm. per kilogram body weight per day, while the infants on the higher osmolar formulae excreted 18.0 mOsm. per kilogram body weight per day. The "excess" renal water was greater with the lower osmolar feeding.

The data from five infants whose water intake was reduced and who were then fed formulae of varying osmolar content show a greater weight loss when on a high osmolar formula (4.3% vs. 1.6% body weight), which is a reflection of the greater urine volume. It is postulated that if renal water in excess of obligatory expenditure is not available, then the higher solute loads of the formulae could be the determining factor in altering the state of body hydration.

The data suggest that consideration needs to be given to the solute composition of the formula in the newborn period in order to maintain a greater margin of safety with regard to hydration. A similar consideration must be given in feeding dehydrated and sick infants where renal concentrating capacity may be reduced.

68. Pulmonary Complications of Congenital Heart Disease in Infants. EDWARD C. LAMBERT, M.D.*; Y. RAMON PEREZ, M.D.,* and PETER VLAD, M.D.,* Departments of Pediatrics and Radiology, University of Buffalo and the Children's Hospital, Buffalo, N. Y. Introduced by Mitchell I. Rubin.

This study was undertaken to determine the incidence, distribution, and significance of atelectasis and emphysema in 165 consecutive infants with severe congenital cardiac malformations of various types. In addition, an analysis was made of the level of the diaphragm in an attempt to determine the incidence of depression of this structure in the same series of patients. Proof of the cardiac diagnosis consisted of autopsy findings (13 cases) or surgery (27 cases). An equal number of controls of similar age distribution were used for comparison. To the best of our knowledge, no such detailed study concerning these points has been previously made.

Lobar atelectasis or emphysema was found in 9% of the total series of infants with heart disease. However, these complications occurred in 29%, or almost one-third, of the 49 infants with either a patent ductus or a large ventricular septal defect. Examples will be presented, together with a complete tabulation of the types of complications and their frequency distribution among the various cardiac malformations.

Although there were instances of atelectatic involvement of each of the lung lobes, the right upper lobe was most commonly affected. Two cases of lobar emphysema were observed: in one of these the middle lobe was involved; in the other, the left upper lobe.

Arbitrarily, cases of either congenital anomalies of the lungs or bronchial tree or of acquired pulmonary disease, such as infection or foreign body, were excluded from the study. We believe, therefore, that the changes observed in these infants were secondary to the cardiac pathology.

The left-sided complications may be explained by the presence of an enlarged heart or pulmonary artery impinging on the left bronchus. We are unable to explain the complications occurring in the right lung. In three cases, the atelectasis cleared following successful cardiac surgery. In four instances, it disappeared spontaneously. If surgery is to play a part in management of infants with these complications, the primary concern should be directed toward the heart.

The level of the diaphragm was arbitrarily determined by measurement of its maximal height above the line connecting the anterior and posterior sulci as visualized in the lateral roentgenogram. A statistically significant correlation between heart disease and depression of the diaphragm was found when measurements from this group were compared with those obtained from the controls without heart disease. The mean value of the diaphragm level for the cases was 11 mm. The same value for the control group was 19 mm.

Further analysis showed an inverse relationship between the diaphragm level and the heart size as measured by the cardiac-thoracic ratio. Anomalies having increased pulmonary flow and pulmonary hypertension were most frequently associated with the flattening of the diaphragmatic curve. We believe that this diaphragmatic depression indicates secondary impairment of pulmonary function. In addition, it may mislead the clinician into believing the liver is enlarged when in fact it is only displaced downwards. The latter point is important with respect to the clinical determination of heart failure. In infants with heart disease, it is important to take into account this frequent finding of depression of the diaphragm and to consider carefully the roentgenographic picture before arriving at a diagnosis of heart failure.

69. Wilson's Disease Without Neurological Manifestations: An Unsuspected Cause of Cirrhosis in Children. ANDREW SASS-KORTSAK, M.D.*; MORRIS CHERNIAK, M.D.,* and MARY LOUISE HOSF, B.A.,* Department of Pediatrics, Faculty of Medicine, University of Toronto and The Research Institute, The Hospital for Sick Children, Toronto, Canada. Introduced by A. L. Chute.

In the course of a study into the etiological factors responsible for childhood cirrhosis, four cases were discovered to be suffering from the hepatic form of Wilson's disease.

Three of these patients were referred to us with the diagnosis of infectious hepatitis. The clinical course and the results of liver function studies

* By invitation.

were compatible in all four with the picture usually seen in subacute or chronic hepatitis. All of them died in hepatic coma two months to four years following the appearance of the first sign of liver disease. Neurological symptoms were repeatedly looked for but never found. The pathological finding of postnecrotic scarring of the liver with sequelae was also compatible with the diagnosis of posthepatitic cirrhosis.

The correct diagnosis was suspected only after abnormalities of copper metabolism were detected. Subsequently slit-lamp demonstration of Kayser-Fleischer rings confirmed the diagnosis in the three cases so examined.

Two of the four cases, a pair of brothers, ran a more chronic course with duration of symptoms for four years. Both showed only moderately high urinary copper excretion which however increased further under the effect of BAL and EDTA. Their serum copper levels were in the high normal range and, as an even more unusual finding, serum levels of ceruloplasmin were normal. However, the presence of Kayser-Fleischer rings in both, and grossly elevated tissue copper levels in the one case analyzed, leave little doubt of the diagnosis.

The other two patients ran a more acute course and died six weeks and three months, respectively, after the onset of symptoms referring to liver disease. Both had extremely high urinary copper excretion, over 1000μg. per 24 hours. In one of these, serum and cerebrospinal fluid copper levels were unusually high. The other patient's serum copper was typically low in association with a low serum ceruloplasmin level.

Aminoaciduria was present in all four patients. An increased phosphate clearance was demonstrated in the one patient so tested, while all four had markedly decreased serum phosphorus levels.

Tissue copper analyses were performed in two cases. Both showed very marked increase of copper in the liver and kidney. The brain copper content, although above normal, was relatively less increased. The latter findings may be an explanation for the absence of neurological symptoms in these patients.

These findings emphasize the need for a study of copper metabolism in the investigation of otherwise unexplained childhood cirrhosis. Such a line of study may be rewarding even in cases where history and clinical findings suggest posthepatitic cirrhosis. Unfortunately the findings related to the abnormalities of copper metabolism in our limited number of cases seem to indicate the necessity for a detailed study of copper metabolism since no one of the individual tests appeared completely reliable.

70. The Pattern of Folic Acid Deficiency Development During Folic Acid Antagonist Therapy in Children With Acute Leukemia and Neuroblastoma. A. LEONARD LUHBY, M.D.*; JACK M. COPPERMAN, Ph.D.*; DAVID N. TELLER, B.S.*; JEFFERY B. WENIG, B.S.,* and ROBERT FELDMAN, M.D.,* Department of Pediatrics, New York Medical College, Flower and Fifth Avenue Hospitals, New York. Introduced by Lawrence B. Slobody.

Children with acute leukemia and other malignancies have been treated with folic acid (PGA) antagonists for the past 10 years with varying success. There have been no previous studies relating responses achieved, however, to the development of antagonist-induced PGA deficiency, presumably the modus operandi of the treatment, because of a lack of adequate methods to assess PGA deficiency.

This report presents observations on the pattern of development of PGA deficiency, as indicated by urinary formimino-L-glutamic acid (FIGLU) excretion, in children with acute leukemia and neuroblastoma during PGA antagonist therapy. FIGLU, a normal amino acid intermediate in glutamic acid formation, has recently been shown to occur in the urine in a variety of clinical PGA deficiency states and to be a useful biochemical criterion of such deficiencies.

The patients received daily oral doses of amethopterin of 1.25 to 3.75 mg. for periods of 28 to 78 days. The amount of FIGLU in urine was measured indirectly by comparing microbiological assays for "glutamate" in heated and unheated aliquots of daily 24-hour urine collections. Urine normally contains glutamic acid and glutamine. Both "glutamates" are detected by this assay with Lactobacillus arabinosus. FIGLU per se does not support growth of the test micro-organism, and is thus not detectable, until it is converted to glutamic acid. Heating urine accomplishes this conversion but at the same time eliminates glutamine. Thus, if appreciable amounts of FIGLU are present, heated urine shows increased "glutamate" compared to unheated urine, whereas heated urine, normally, shows decreased "glutamate" due to the loss of glutamine. Because of variation in glutamate excretion from one person to the next, results expressed as by the ratio of heated to unheated urine "glutamate" assays (H/U) were most meaningful for comparative purposes. Normally, ratios varied from 0.2 to 0.5. Values of 0.9 or higher indicate the presence of considerable quantities of FIGLU. Prior to PGA antagonist therapy, the patients studied had ratios of 0.5 or lower.

Results showed a direct relationship between the dosage of PGA antagonist and the subsequent urinary FIGLU excretion. Patients varied con-

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siderably, however, with regard to time and dose required for development of comparable FIGLU excretion. With antagonist doses of 2.5 mg. per day, the time required to reach glutamate H/U assay ratios of 0.9 varied from two to five weeks. Peak ratios were of the order of 2.0. With the same dosage and duration of administration, higher ratios were usually found in acute leukemia than in neuroblastoma. A one-to-three-day lag period occurred between subsequent decrease or increase of antagonist and the corresponding decline or rise of FIGLU excretion.

In acute leukemia, total peripheral blood white cell counts varied inversely with the urinary FIGLU excretion. The white cell count did not fall as far nor show as constant a relationship to the FIGLU excretion in neuroblastoma as in acute leukemia.

These studies demonstrate that children with acute leukemia and neuroblastoma vary in their susceptibility to induction of PGA deficiency by a PGA antagonist. In general, the deficiency was more readily induced in children with acute leukemia than in those with neuroblastoma.

71. A Follow-Up Study of an Infant With Anaclitic Depression. JULIUS B. RICHMOND, M.D., and LEONARD HERSHER, Ph.D.,* State University of New York College of Medicine, Syracuse, N. Y.

The syndrome of anaclitic depression, or hospitalism, was first described among infants who experienced separation from their mothers in an institutional or hospital environment. The principal symptoms of the disorder are reported as listlessness and unresponsiveness to stimulation. Many of these infants stare with wide-open expressionless eyes, show extreme anxiety when approached, and generally fail to gain weight or to thrive. Recent case reports of infantile depression in home-reared children have suggested that the development of this condition is not solely a consequence of institutional life, but of any environment during the first year characterized by lack of stimulation and/or maternal separation.

Although some investigators have reported dramatic and rapid improvement when these babies were removed from the institutional environment and placed under the care of foster mothers, until recently no follow-up studies have been published on the subsequent development of children who have experienced a period of depression during infancy. Several controlled investigations, notably Goldfarb's, have demonstrated long-term intellectual and personality effects of institutionalization during the first three years of life, but it is unknown whether any of the children reported in these studies had as infants shown the symptoms of hospitalism.

This is a follow-up study of a child who was hospitalized at 13 months of age because of severe malnutrition, retarded development, extreme anxiety when approached, autoerotic behavior, and frozen body posture. Medical studies revealed no organic etiology for the clinical picture.

The baby was cared for primarily by a single nurse and under this care she improved rapidly in weight, behavioral development, and social responsiveness. At 21 months she was placed in a foster home and there, after a difficult period of readjustment, she continued to improve.

The child has remained in the foster home and has been examined periodically since placement, up to her present age of 5½ years. Her intellectual development reached normal limits by 3 years, and has continued to develop normally. Her personal-social behavior, however, is characterized by many of the signs noted by Goldfarb in institution-reared children.

The child is restless, hyperactive, and unable to concentrate. Although her kindergarten teacher considers her bright and attractive, her inability to join with a group of other children in a single project prevents her from meeting the demands of more orderly first grade school work.

She craves constant assurances of affection, is very fearful of short-term separation from her foster mother, yet is highly independent, aggressive, and resistant to adults and to children. She shows no guilt upon breaking rules, but becomes deeply upset and depressed when punished.

In sum, she shows relatively normal intellectual growth (unlike Goldfarb's cases), but her personality suggests a development similar to Goldfarb's institutionalized children and to Bowlby's "affectionless character." Further follow-up observations are planned in order to observe whether the personality characteristics noted may be further influenced by good foster home placement.

72. Sickle-Cell Trait Associated with Hereditary Hemolytic Diseases. A. H. TUTTLE, M.D.*; J. A. SHEFFIELD, M.D.,* and H. H. LONG, M.D.,* University of Tennessee College of Medicine, Memphis. Introduced by J. N. Etteldorf.

Two families have been studied who harbor both the genes for Hgb S and for other hereditary hemolytic disease. In one family, two of five children have had a severe hemolytic anemia detected in the neonatal period. One of the children has normal hemoglobin, the other shows a sickle-cell trait. One child also has a significantly high number of hyperlobulated neutrophilic leucocytes. In each, splenectomy resulted in a partial correction of

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the previously severe anemia. Outstanding features of the anemia are bizarre morphology of the erythrocytes, marked increase in osmotic fragility as determined quantitatively both before and after incubation, and significant autohemolysis upon incubation.

The only hematologic abnormality detected in relatives was sickle-cell trait in one parent and two other siblings and hyperlobulation of the neutrophiles in one parent and one other sibling. Serologic studies of the patients, their siblings, and their parents did not suggest false parentage and no unusual antigen-antibody system involving the erythrocytes was detected.

In the second family of five children, one child and the father have HgB S trait and hereditary spherocytosis, the mother and three children have Hgb S trait, and the one remaining child has homozygous Hgb S disease. The erythrocyte morphology and reduced resistance to hypotonic saline as quantitatively determined are typical of hereditary spherocytosis in the father and the one child. Historically, the father was severely anemic when a child. He is now polycythemic despite the fact that he has a markedly enlarged spleen. Response to a recent splenectomy in the one child with spherocytosis-sickle-cell trait has been excellent. The osmotic fragility of two of the other three children in the family with sickle-cell trait is slightly increased before and after 24 hours incubation at 37 C. Although the erythrocyte morphology and hemoglobin levels in these two children do not suggest typical hereditary spherocytosis, they may represent a mild variant of this condition, since erythrocytes of persons with sickle-cell trait showed a slight but definite decreased fragility in parallel experiments.

73. Renal Bicarbonate Excretion in Children with Renal Acidosis. DOMAN KEELE, M.D.*; MALCOLM HOLLIDAY, M.D.,* and THOMAS EGAN, M.D.,* Department of Pediatrics, University of Pittsburgh, School of Medicine, Pittsburgh. Introduced by E. R. McCluskey.

The development of renal acidosis in advanced renal disease may be related to any of the following considerations: (*a*) glomerular insufficiency such that plasma anion concentration other than bicarbonate or chloride must increase to effect adequate excretion; (*b*) glomerulotubular imbalance such that, for a given nephron, there is insufficient hydrogen ion excretion to reabsorb all bicarbonate and maximally acidify urine; (*c*) the development of frank bicarbonate excretion at plasma bicarbonate levels below normal, and (*d*) failure to secrete ammonia. The first is generally evidenced by a low plasma CO_2, and an elevated concentration of plasma undetermined anion. The latter three would be evidenced by a low plasma CO_2, and an elevated plasma chloride concentration. The following report concerns bicarbonate excretion studies in children with renal acidosis from long standing de Toni-Fanconi renal disease, who had developed glomerular insufficiency with elevated urea nitrogen. There were six studies in four children, aged 5 to 14 years who had greatly reduced glomerular filtration rates (between 4 to 16 cc. per minute). Elevation of undetermined anion was observed in each instance so that glomerular insufficiency accounted in part for the acidosis. However, serum chloride was also elevated and some impairment of bicarbonate reabsorption was postulated. Roberts has already reported that bicarbonate reabsorption in relation to filtered bicarbonate is normal in advanced renal disease, i. e., 2.4 to 2.8 mEq/100 cc. G. F. R. In three of the presently reported studies where reabsorption at near normal levels was tested, this appeared to be the case, that is, frank bicarbonate excretion did not appear until plasma level reached normal. On the other hand, in five instances small but increasing amounts of bicarbonate were excreted as bicarbonate was infused to elevate plasma bicarbonate concentration from low to normal levels.

This was not the case in the studies of normal persons reported by Pitts and in the one child tested here during repair of severe diabetic acidosis by comparable bicarbonate infusion. In the subjects with no renal disease, urine total CO_2 concentration was consistently below 2.5 mEq. per liter until plasma levels exceeded 24 mEq. per liter. In the children with renal disease, urine bicarbonate concentrations were above 3 mEq. per liter when plasma concentration was 100 mEq. per liter and rose gradually up to 14 with plasma levels below 20. Urine bicarbonate concentrations in excess of plasma concentrations did appear until alkalosis resulted.

It is inferred from these studies that a glomerulotubular imbalance exists such that bicarbonate reabsorption does not go to completion in all nephrons under conditions where it would do so in the normal.

Whether this is specific to this disease throughout its course or is a general manifestation of advanced kidney disease cannot be determined from these data. These findings are in accord with other examples of demonstrated glomerulotubular imbalance with respect to glucose, PAH, and other substances in advanced renal insufficiency from any cause.

Its importance as a contributing cause to base loss and to the renal acidosis is self-evident. The apparent paradox that reabsorption rate is normal at normal plasma levels but excretion is increased at low to normal plasma levels can be resolved by

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noting that the quantity excreted is but a small fraction of that filtered.

No studies on ammonia excretion were made.

74. The Fate of Heterologous Plasma Proteins in the Newborn Rabbit and in Human Infants. DONALD V. EITZMAN, M.D.,* and RICHARD T. SMITH, M.D.,* From the Department of Pediatrics, University of Texas, Southwestern Medical School, Dallas, Texas. Introduced by E. L. Pratt.

With modern feeding practices, the newborn infant is the recipient of a variety of proteins derived from heterologous species and often in large quantities. In view of the demonstration in several previous studies, and in our own unpublished data that such proteins may be absorbed by the newborn infant, particularly in the presence of gastrointestinal disorders, it was of interest to investigate the fate and handling of a variety of defined heterologous proteins in the neonatal period. For the experimental studies, neonatal rabbits were given single intraperitoneal injections of varying amounts of crystalline bovine albumin, human γ-globulin, human albumin, or a macroglobulin and the amount remaining in the serum at intervals up to 50 days was determined by quantitative immunochemical techniques. Semilogarithmic plots of the resultant data revealed that each protein had a constant and exponential disappearance rate from the serum, no immune phase of degradation being observed and no antibody being formed even at an age when immunological maturity is otherwise demonstrable. Both bovine albumin (half-life=3.5 days) and human γ-globulin (half-life=6.7 days) half-lives were approximately one-half of those found in the immunologically unresponsive adult rabbit (albumin half-life=6.7 days; γ-globulin half-life=8.5 days), even when corrected for growth of the protein space. By three months of age the unresponsive animals cleared albumin at the adult rate. Slower rates of degradation were observed when amounts of bovine albumin sufficiently large to induce immunological unresponsiveness were given as compared to those not producing a prolonged unresponsive state. Since no evidence of excretion of the proteins is available and since they appear to be handled similarly to homologous proteins, it seems probable that these data indicate a higher rate of turnover of plasma proteins in neonatal rabbits as compared with older animals, possibly related to their extremely high rate of growth.

Opportunities to determine the handling of heterologous proteins in human infants have been afforded in six infants who required large quantities of horse γ-globulin as tetanus antitoxin in the treatment of tetanus neonatorum, or as prophylaxis in the case of dirt-contaminated wounds. Serial quantitative immunochemical study of the serum of these infants has yielded the following information thus far. 1. Three infants received 30,000 to 100,000 units of antitoxin at 1 to 7 days of age. Demonstrable horse γ-globulin is still present in the serum of one infant at 30 days and in another infant at 134 days after an exponential type of disapperance (half-life=18 days); no demonstrable antibody against any component of the antitoxin has been observed. 2. Faster disappearance rates (half-life=approximately 8 days) were found in two infants, 4 and 6 weeks of age, who received 30,000 and 10,000 units of antitoxin, respectively, but no antibody formation was observed. The question of whether these infants who received the large amounts of antitoxin shortly after birth are immunological unresponsive has not been answered, but it appears that they catabolize this protein in a manner qualitatively similar to the neonatal rabbit which has received an amount of protein known to induce unresponsiveness.

75. Iodinated Compounds in Thyroid Disturbances, Observed in Autoradiograms. WM. A. REILLY, M.D.; K. G. SCOTT, Ph.D.*; G. L. SEARLE, Ph.D.,* and J. N. CASTLE, A.B.* From the Pediatric Department, University of California, School of Medicine, and the Radioisotope Service, Veterans' Administration Hospital, San Francisco.

Euthyroid (six cases), goitrous hypothyroid (six cases), hyperthyroid (two cases), hypothyroid (two cases) and simple goitrous children (two cases) were given an I^{131} tracer ($<3\mu$c. per kilogram). Ethanol extractions of plasma, urine, and feces were run in n-propanol, NH_4OH on ascending chromatograms; autoradiograms were made from these at various times from 24 to 96 hours.

A comparison of the order of appearance of various thyroid products in plasma showed that mono- (t_1) and diiodotyrosine (t_2) are observed at early intervals in hyperthyroid and simple goiter cases. These compounds appeared at a later time and less often in euthyroids and goitrous hypothyroids. Thyroxine (t_4) was evident at early time intervals in the hyperthyroid cases, later in euthyroids, still later in the goitrous hypothyroids, and not at all in the cases of simple goiter. Unidentified I^{131} compounds were evident at late intervals, most consistently in the goitrous and acquired hypothyroids, but occasionally in the euthyroids.

The findings in urine and feces were similar though less marked than those in plasma.

Qualitative information about iodinated compounds in autoradiograms indicated the following: the expected rapid synthesis was easily detected in hyperthyroidism; the early appearance of t_1 and t_2

* By invitation.

in simple goiter with the absence of t_4 was interesting as a possible metabolic abnormality, and the consistent presence of unidentified compounds in the goitrous hypothroids was also an interesting finding.

76. Observations on High and Low Protein Diets. SELMA E. SNYDERMAN, M.D.*; AUDREY BOYER*; MAURICE KOGUT, M.D.,* and L. EMMETT HOLT JR., M.D., Department of Pediatrics, New York University-Bellevue Medical Center, New York.

Although breast milk is generally accepted as furnishing a desirable quantity of protein for the full-term infant, its adequacy in this respect for the premature has been questioned by a number of investigators and protein intakes in excess of 2.0 to 2.5 gm. per kilogram are commonly recommended in this country. Often twice as much is given. These higher recommendations are based on the fact that the body of the premature is poorer in nitrogen than that of the term infant and that when the premature's nitrogen intake is increased his nitrogen retention is also substantially increased.

It seemed possible that some light might be thrown on the question of desirable protein intakes by feeding infants at levels both higher and lower than those commonly employed. We have, therefore, fed one group of prematures a formula providing 2 gm. of protein per kilogram and a second group a formula providing 9 gm. per kilogram. The caloric intake in the two groups was comparable. These feedings were continued throughout the period of stay in the premature unit, usually five to six weeks. Observations were made on the general health, weight gain, nitrogen retention, and on various nitrogenous constituents of the blood.

The general health was well maintained in both groups. Only one serious infection was encountered, an attack of herpetic keratitis, which developed in one of the infants on the high protein feeding. The weight curves in both groups conformed to standards for infants of comparable birth weights. Nitrogen retention in the low protein group ranged between 200 and 250 mg. per kilogram, figures which are generally regarded as satisfactory for term infants. Much higher retentions were, however, observed on the high protein diets, in some instances reaching 800 to 1000 mg. per kilogram. Since cutaneous nitrogen losses were not measured in our first studies, it was thought possible that these high retention figures might be spurious; however, observations made on cutaneous nitrogen losses indicated that these losses were relatively small. An unexpected finding was the persistence of nitrogen retention figures at these high levels for periods as long as a month without any reduction.

The location and nature of the additional nitrogen retained on the higher protein diet and its potential value are interesting questions which cannot be adequately answered at the present time. It was found that higher values of nonprotein nitrogen of the blood would explain part of the retention. The urea and amino acid fractions were particularly affected. Some alterations in the plasma amino acid pattern were also observed.

77. The Plasma Osmolar Concentration in Premature Infants. HANS. G. KEITEL, M.D.,* From the Departments of Pediatrics, Jefferson Medical College, Philadelphia, and Howard University, Washington. Introduced by James Arey.

The infant is in a precarious position in respect to maintaining normal hydration because, relative to the adult, his maximum urine concentration is limited and the rate of water loss by the insensible route is increased. If he is given a diet containing a high content of substances which must be excreted by the kidney, if he develops fever, is exposed to a high environmental temperature or has a low fluid intake, large demands are made on his water reserve.

The present study was performed to determine the effect of the administration of isocaloric-isoaqueous formulae of varying protein and mineral content on the osmotic pressure of the plasma of premature infants. The cryroscopic method was used to determine the osmotic pressure (milliosmolars) of plasma. The analytical accuracy obtained was within 2%. The conclusions derived are based on data obtained from over 300 observations.

Premature infants ranging from 4 days to 3 weeks of age had plasma containing, on the average, 276 mOsml. (range, 265 to 287) while receiving a preparation of milk which provided 3.0 gm. of protein per kilogram per 24 hours, while on a protein intake of 4.5 gm. per kilogram they had 283 mOsml. (range, 267 to 296), and on a protein intake of 6.0 gm. per kilogram, the plasma contained 286 mOsml. (range, 276 to 320). Normal adults have plasma which contains 280±5 mOsml. Infants weighing from 2 to 4 lb. did not develop hyperosmolarity on the high protein-mineral intake any more frequently than did infants weighing over 4 lbs.

Infants with a urinary concentration maxima of 600 mOsml. and with a plasma concentration of 310 rather than 280 mOsml. are compelled to use about 4% of their body water to excrete the added solutes dissolved in their body water. This places the infant in an undesirable position if he suddenly develops thirsting.

These data lend further support to the concept that foods, such as human milk, which contains a "physiologic" content of minerals and protein are

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preferable to milks with a high protein content for the feeding of premature infants.

78. Hemoglobin and Serum Iron of Infants Fed Milk Mixtures With and Without Added Iron. A. MARSH, M.D.*; H. LONG,* and E. STIERWALT, R.N.,* Department of Pediatrics, University of Kansas Medical Center, Kansas City, Kans. Introduced by D. C. Darrow.

A longitudinal feeding study has been carried out on full-term and premature infants from birth to 9 months of age. The study was designed to (1) find the effect of iron added to milk upon the hemoglobin and serum iron values in normal full-term and premature infants, and (2) find the effect of iron added to milk in the treatment of mild cases of iron deficiency anemia. Infants were assigned at birth to one of the following three feeding regimes: (1) a milk mixture to which 12 mg. elemental iron had been added to each 28 ounces of the mixture, ready for consumption (28 full-term and 16 premature infants); (2) the same milk mixture as in (1) but with no additional iron (24 full-term and 17 premature infants); (3) a milk mixture based on evaporated milk (21 full-term and 11 premature infants). The milk mixtures were isocaloric and the infants were allowed no solid foods except an especially prepared cereal which contained practically no iron. Infants in whom the hemoglobin fell below 8.0 gm. were shifted to Feeding Regime 1 and their hematologic response observed. It was necessary to add iron to the diet of (1) none of the infants, full-term or premature, receiving the milk mixture with added iron from birth (Feeding Regime 1); (2) one full-term and 7 premature infants in Feeding Regime 2, and (3) one full-term and eight premature infants in Feeding Regime 3. Both full-term infants were 7 months of age at the time of onset of treatment and the premature infants were an average of 4½ to 5 months of age. Response to the milk mixture with added iron was prompt and adequate (an average hemoglobin rise of 2.8 gm. in the first month after onset of treatment).

The study period lacks six weeks of completion, but data which have been collected thus far indicate that infants who have been fed a milk mixture containing added iron maintain higher hemoglobin and serum iron values than those who were fed no supplemental iron. Full-term infants who were fed an iron enriched milk mixture had hemoglobin values which were 1 gm. higher at 6 months of age and an average of 2 to 3 gm. higher at 9 months of age than either control group. The difference in premature infants is more striking, i. e., 1.0 to 1.5 gm. at 4½ months and 3 to 4 gm. at 9 months. All serum iron values were lower than those seen in adults, but average serum iron values of the infants who were fed the iron enriched milk mixture were consistently higher than the control groups. Values were double and triple those of the control groups at 9 months in full-term and premature infants, respectively.

79. Prognosis for Prematures During Infancy. WILLIAM T. NEWSOM,* and LOUISE PESUT,* Department of Pediatrics, Tulane and Louisiana State Universities, New Orleans. Introduced by R. V. Platou.

Prematurity has been the subject of much pediatric consideration and investigation during the past several decades. Great progress has been made in certain areas; however, much remains to be done. For example, inborn hospital mortality rates for premature infants seem now to remain rather constant between 15% and 20% after the first several years of establishing a modern nursery program. Much has been accomplished to improve nursery standards; however, until major additions have been made to our basic knowledge regarding these infants, there seems to be little reason to be optimistic for significant further reduction in these hospital mortality rates. For these reasons, increased attention to some aspects of prognosis for prematures during the early years following discharge from the nursery may be warranted.

Pertinent details for 280 Negro premature infants having a birth weight less than 2000 gm. have been reviewed with particular emphasis on nutritional and hematological status, morbidity, and mortality. Ninety-three of these were sampled from the total population of premature infants born in this hospital during 1953. An "intensive" multidisciplinary survey of these babies was made during 1955. Material from this study suggested a higher incidence of certain disorders than would be expected among term babies. The known mortality rate from discharge to one year of age for these prematures was 5.9%.

Stimulated by this and other defined problems, our premature infant follow-up program was redesigned in an attempt to meet specific needs, to provide certain uniformities in care, and to evaluate total well-being by serial anterospective studies. One hundred eighty-seven infants receiving care in the new program make up the second uniform sample. The known mortality rate from discharge to one year of age for this sample was 3.0%.

Records have also been compared for rehospitalization rates by specific disease category. Serial dietary surveys, some pertinent laboratory studies, more intensive "health education" through group counseling, and other factors of possible prognostic relationship have been evaluated. From these studies, it is suggested that increased attention concerned with organization and utilization of currently available methodology for follow-up care may further improve the prognosis for infants prematurely born.

* By invitation.

80. Mode of Transmission of Familial Ectodermal Dysplasia. ALLEN H. KLINE, M.D.*; J. B. SIDBURY JR., M.D.*; C. P. RICHTER, M.D.,* and J. BILLINGSLY, M.D.,* Department of Pediatrics and Psychiatry, Johns Hopkins Hospital, Baltimore, and Kansas City, Kans. Introduced by Robert E. Cooke.

Hereditary ectodermal dysplasia is not a rare disorder. It is characterized by the triad of anhidrosis, hypotrichosis, and dental hypoplasia. It has been apparent that there is a wide variation in the clinical involvement from case to case, but in general males have consistently been more severely affected than females. Characteristically males exhibiting the anhidrotic form of the disorder have been born of apparently normal mothers. This observation has given rise to the suggestion that the disorder is sex-linked.

A study of the hereditary transmission of familial ectodermal dysplasia was undertaken using a Whelen dermometer to measure the skin resistance over the entire body surface of members of a family representing six generations, some of whose members had familial ectodermal dysplasia. Some of the kindred, who were completely asymptomatic, were shown to have discrete areas, irregular in size, shape, and distribution, which did not sweat. By previous criteria these individuals would have been labeled carriers. The distribution of those affected as determined by skin resistance measurements of the total body surface area suggests that the disease is transmitted as a Mendelian dominant with variable expression and sex-modified.

During the course of this investigation, a new facet to this clinical syndrome was uncovered. Approximately 45% of the affected members of this family, considering those 40 years of age and older, who were examined had a corneal dystrophy. The dystrophy was usually first noticed in the third or fourth decade and was slowly progressive, although none to date have resulted in blindness. There appears to be nothing characteristic about the corneal dystrophy found. In most of those individuals with corneal dystrophy this abnormality would be the most likely reason for them to seek medical advice and hence lead to the diagnosis of the underlying disorder. Secondly, this abnormality serves as an additional genetic marker in this family.

81. Female Pseudohermaphroditism Associated with Cystic Ovaries Containing Luteinized Thecal Cells: A Review of 4 Cases. JOHN F. CRIGLER JR., M.D.,* and JOHN M. CRAIG, M.D.,* Department of Pediatrics and Pathology, Harvard Medical School, and the Children's Hospital, Boston. Introduced by William Berenberg.

Present concepts of embryological sex development suggest that male differentiation requires the presence of androgenic substances either produced by the fetal testis or arising extragonadally, i. e. from the embryonic adrenal or a maternal source. Recently we have discovered in four patients, born with abnormal external genitalia consisting of a hypertrophied clitoris with or without fusion of the labia and the presence of a urogenital sinus, abnormal polycystic ovaries histologically showing luteinization of the thecal cells in three of the four patients. The patient not showing luteinization was 3 years old at the time of operation and therefore not under the influence of gonadotropins. Of the other three, two were newborns and the other was an 11½-year-old patient raised as a boy who had breast development. Surgical exploration revealed normal vagina, uterus, and Fallopian tubes in all patients. Histories have been negative for maternal ingestion of any steroids during pregnancy and for the presence of maternal endocrinopathies. Urinary 17-ketosteroid excretion has been normal for their ages, thus excluding primary adrenal disease. The patients studied at 3 years and 11½ years have not shown clinical evidence of excessive adrenal or gonadal function. Chromosomal sex patterns were female from histological sections studied.

Since there is considerable physiological and biochemical evidence suggesting that ovarian tissue, luteinized thecal cells in particular, is capable of synthesizing virilizing hormones, it seems reasonable to us to suggest that the abnormal genital development seen in these patients is related to the ovarian pathology described. This assumption is further supported by the absence of other sources of extragonadal androgens and by the fact that infants and adults with thecagranulosa-cell tumors may show evidences of virilization which disappear when the tumors are removed. We have recently seen such a case in an 11-month-old girl who had a 1 kg. thecagranulosa-cell tumor. Slices of this tumor have been incubated in another laboratory with C^{14}-labeled acetate and estrogen in order to study its ability to convert these compounds to various intermediates, including testosterone, which are thought to exist in the pathway of estrogen synthesis by endocrine tissues (gonads, placenta, adrenal).

Although we believe that the ovaries in these patients are the source of the hormone producing the abnormal genitalia, it is not possible at this time to assume that the ovary is the site of the primary defect. The possible relationship of this abnormality to that seen in young adults with polycystic ovaries and hyperthecosis of the Stein-Leventhal syndrome will be discussed.

* By invitation.

Abstracts from Current Literature

Acta pædiatrica, Stockholm

Abstracted by William W. Cleveland, M.D.

46, No. 6 (Nov.) 1957

The Bulbar Conjunctival Vascular Bed in Diabetic Children. J. Ditzel and J. Duckers.—p. 535.

A Case of Congenital Friedreich's Disease, with Autopsy. E. Cristensen and J. E. Rasmussen.—p. 553.

An Epidemic Among Swedish Children Caused by Adenovirus Type 3. L. Kjellen, B. Zetterberg, and A. Svedmyr.—p. 561.

The Failure of Newborn Premature Infants to Absorb Antibodies from Heterologous Colostrum. F. Nordbring. —p. 569.

On the Variability of the Clinical Course of Congenital Toxoplasmosis with Special Reference to the Occurrence of Mild Cases. G. Hedenstrom.—p. 579.

The Serum Vitamin B_{12} Levels at Various Ages. A. Killander.—p. 585.

Red Blood Cell Survival in Cyanotic Congenital Heart Disease. B. Jonsson.—p. 595.

A Wilms' Tumour Family. T. Strom.—p. 601.

* Surgical Treatment of Funnel Chest. G. Ekstrom and O. Qvist.—p. 605.

The Correlation Between the Development of the Hypophysial Portal System and the Onset of Neurosecretory Activity in the Human Fetus and Infant. N. Raiha and L. Hjelt.—p. 610.

Infantile Cerebral Palsy: A Sociomedical Enquiry Carried out in the County of Ostfold in Norway 1954-1955. B. Andersen.—p. 617.

Biophysical Analyses of the Formation and Structure of Human Fetal Bone: A Microradiographic and X-Ray Crystallographic Study. G. Wallgren.—p. 619.

Immunization in Whooping Cough. Danish Pediatric Society.—p. 621.

47, No. 1 (Jan.) 1958

The Use of Hibernation in the Bronchoscopic Examination on Infants and Children. Z. Lábas and I. Simkó.—p. 1.

Pathogenic Bacteria in the Pharynx and Naso-Pharynx of Hospitalized Children and Their Relation to Clinical Infection. G. Laurell, G. Tunevall, and G. Wallmark.—p. 34.

Infections with Poliovirus Types 2 and 3 in Day Nurseries and an Orphanage. A. Svedmyr, M. Gullmar-Arvidsson, and G. von Zeipel.—p. 46.

Complications of Intracutaneous BCG Vaccination in Newborn Infants. M. R. Stoppelman and E. Drion.—p. 65.

* The Hyaline Membrane Disease: A Review of Earlier Clinical and Experimental Findings and Some Studies on the Pathogenesis of Hyaline Membranes in O_2-Intoxicated Rabbits. R. Berfenstam, T. Edlund, and L. Zettergren.—p. 82.

Surgical Treatment of Funnel Chest.—An experience with 40 children undergoing surgery for correction of funnel chest is described. Symptoms noted to be referable to this condition were dyspnea, fatigability, and susceptibility to respiratory infections and cough, while clinical study of the patients revealed varying degrees of impairment of respiratory and circulatory function. Another common complication was kyphosis. The surgical technique employed is described and is reported to have yielded satisfactory results with improvement in the majority of patients. From this experience the authors recommend that the procedure be done at the age of 3 to 6 years and set forth the following indications for surgical correction: (1) signs of respiratory and/or circulatory disturbance, (2) sternal depression of a severity implying risk of future spinal deformity, (3) strong cosmetic reasons. "A child, and probably also an adult, prefers a scar on the chest to a deep and easily detectable depression."

The Hyaline Membrane Disease: A Review of Earlier Clinical and Experimental Findings and Some Studies on the Pathogenesis of Hyaline Membranes in O_2-Intoxicated Rabbits.—A brief review of the problem of hyaline membrane disease as regards both the clinical picture and the various theories as to its etiology is presented. This is an introduction to the presentation of the authors' own investigations, in which adult rabbits were maintained in concentrations of oxygen from 70% to 80% until death took place, following which the lungs were studied for evidences of hyaline membranes. Such membranes, having the same localization, morphology, and staining characteristics as those demonstrated in newborn infants, were found in 80% of the animals, with atelectasis in 60%. It was concluded that the formation of these membranes was probably preceded by an increased capillary permeability in the

lungs and that the material constituting the membranes was derived from plasma components, including carbohydrates. These findings in relationship to other theories of pathogenesis of hyaline membrane disease are discussed.

Blood, New York

Abstracted by Audrey K. Brown, M.D.

12, No. 10 (Oct.) 1957

Specific and Cross-Reacting Antibodies in ABO Heterospecific Twin Pregnancy. Wolf W. Zuelzer, Flossie Cohen, and Abner R. Robinson.—p. 883.

Paroxysmal Cold Hemoglobinuria with Positive Treponema Immobilization Test: Report of Case. N. Milic.—p. 907.

* Syndrome of Hypogammaglobulinemia, Splenomegaly and Hypersplenism. Ananda S. Prasad, E. Reiner, and C. J. Watson.—p. 926.

A Possible New Thromboplastin Deficiency Occurring in Five Siblings. Anna Marie Chirico and Arthur E. McElfresh.—p. 933.

12, No. 11 (Nov.) 1957

Leukocyte Antibodies in Human Sera and in Immune Rabbit Sera. Roy L. Walford, E. Taylor Peterson, and Patricia Doyle.—p. 953.

The Effect of Inflammation on the Utilization of Erythrocyte and Transferrin Bound Radioiron for Red Cell Production. Emil J. Freireich, Aaron Miller, Charles P. Emerson, and Joseph F. Ross.—p. 972.

Physiochemical Properties of Circulating Red Blood Cells of Lethally X-Irradiated Mice Treated with Rat Bone Marrow. Takashi Makinodan and Norman G. Anderson.—p. 984.

Studies of Plasma Erythropoietic Factor in Anemic Human Patients. T. C. Prentice and E. A. Mirand.—p. 993.

* The Postnatal Synthesis of Fetal Hemoglobin: I. Some Studies in Newborn Goats Using Radioactive Fe^{59} and Glycine-2-C^{14}. H. K. A. Visser, T. H. J. Huisman, and M. G. Woldring.—p. 1004.

Unique Sequence of Pernicious Anemia, Polycythemia and Acute Leukemia. Chris J. D. Zarafonetis, Robert L. Overman, and Lyndall Molthan.—p. 1011.

The Behavior, as Regards Shape and Volume, of Human Red Cell Ghosts in Fresh and in Stored Blood. Eric Ponder and Delia Barreto.—p. 1016.

Syndrome of Hypogammaglobulinemia, Splenomegaly and Hypersplenism.—Two cases of splenomegaly with hemolytic anemia due to hypersplenism and associated with acquired idiopathic hypogammaglobulinemia are described. The splenomegaly is believed due to reticulum-cell hyperplasia in response to repeated infections related to absence of γ-globulin. Marked hematologic improvement resulted in both cases from splenectomy.

A review of the literature indicates that this syndrome is fairly common among the cases of acquired hypogammaglobulinemia reported.

The Postnatal Synthesis of Fetal Hemoglobin: I. Some Studies in Newborn Goats Using Radioactive Fe^{59} and Glycine-2-C^{14}.—An interesting study was made in newborn goats of the postnatal synthesis of fetal hemoglobin.

With use of the spectrophotometric alkali-denaturation method of Jonxis and Visser (and taking into account that in the goat adult hemoglobin is more resistant than fetal, which is denatured in 12 minutes), it was found that about 60% of hemoglobin F is present on the first day of life in the goat, while at 60 days only 5% remains. Hemoglobin F was not found in the circulating blood for a few days after exchange transfusion in two animals so studied, but in the next few weeks up to 20% of this component was found.

Uptake of radioiron and radioactive glycine was studied in the adult and fetal hemoglobins in untreated newborn goats as well as in two goats who received exchange transfusion. Maxima of specific activity of radioiron in adult hemoglobin occurred in untreated newborn goats at the 12th day, of C^{14} at the 6th day, and of radioiron in "exchanged" goats at the 8th day. Maxima of the specific activity of radioiron and C^{14} in the fetal hemoglobin in the untreated goats occurred at a later time as compared with the adult hemoglobin, that is, at 32 and 24 days, respectively, while in the "exchanged" goats the maximum for Fe^{59} in the hemoglobin F was attained at about the same time as for the hemoglobin A (eighth day).

The reappearance of hemoglobin F after exchange and the specific activity of hemoglobin F are direct indications of synthesis of hemoglobin F after birth.

Boletín médico del Hospital infantil, Mexico, D. F.

Abstracted by Mary Allen, M.D.

14, No. 6 (Dec.) 1957

The Sensitivity of S. Typhus, S. Murine Typhus, Sh. Flexner, and Enteropathogenic E. Coli to Chloramphenicol to Tetracycline, and to a Combination of These Antibiotics. Jorge Alarte and Otilia Mayes.—p. 589.
Sensitivity of Micrococcus Pyogenes Var. Aureus Coagulase Positive to Six Antibiotics: A Study of 58 Strains Recently Isolated from Hospitalized Children. Jorge Alarte and Georgette Figueredo.—p. 597.
Antibiotics and Staphylococcus Sensitivity in Mexico. M. Ruiz-Castaneda, Lydia Vergas, Emitio Escarzoga, Antonietta Moreno, and Rosario Garcia.—p. 605.
Observations Concerning Diagnosis and Frequency of Amebiasis and Other Parasites in Children with Diarrhea in Mexico City. Francisco Biogi, Faustno Navarrete, and Efigenia Rabledo.—p. 617.
* Auditory Hypoacuity in the Child. Ramon del Villar.—p. 627.
Hydrometrocolpos. Joaquin A. de la Torre.—p. 647.
The Organ of Shock (Allergic). Jose Luis Cortes.—p. 651.

15, No. 1 (Feb.) 1958

Relation of Serial Osmolarity to the Nutritional State of the Child. Rafael Soto, Gustovo Gordillo, Francisco Uribe, H. Julros, and Gloria Merinier.—p. 3.
Physiopathology of Salmonellosis: Serum Proteolytic Activity in Children with Typhoid Fever. Jesus Kumate R., Lazaro Benivides V., Virginia Vasquez, Mercedes Rodriguez, and Julio Canillo.—p. 13.
Prophylactic Effects of Isoniasid on Primary Tuberculosis in Children. Luis Berlorza Berunen, in cooperation with U. S. P. H. S. and Hospital infantil, Mexico, D. F.—p. 25.
Blood Picture in Healthy Children Living in Mexico City (2300 Meters Above Sea Level). Judith Vasquez, Rafael Soto, Olga Castrejon, and Samuel Dorantes.—p. 53.
* Some Clinical and Epidemiological Aspects of Intoxication Due to Drugs Commonly Used in Infancy. Lazaro Benivides, Luiz Gomez Orozco, Enrique Rodriguez Diez, and Armondo Franco Gomez.—p. 75.
Medical Intoxication in Infancy: Report of Two Cases. Armando E. Franco Gomez and Ildefonso Benivides.—p. 89.
Some Aspects of Treatment of Hemolytic Disease of the Newborn Due to Rh Factor. Luis Torregosa.—p. 113.
Anorectal Malformations. Francisco Beltran Brown.—p. 121.

Auditory Hypoacuity in the Child.—The author discusses the anxiety of parents regarding the hard-of-hearing child and the deaf child and the need for thorough examination by teams of specialists. The pediatrician may need the help of an otologist, neurologist, psychiatrist, and an audiometry technician. A hearing defect may have its origin in a defect in conduction, transmission, perception, or interpretation. It may be functional or organic. There may be psychological deafness or psychological aspects due to organic defect. There should be a careful history, observation of the child's behavior, and a thorough clinical examination.

The author warns against the indiscriminate use of such antibiotics as streptomycin and neomycin, which may cause irreversible damage. Salicylates and quinine are also mentioned in this respect, since they as well as antibiotics may cause degeneration of the cochlear or of the eighth cranial nerve.

Conduction may be poor because of such simple things as wax in the canal; the causes range in severity to external auditory exostoses or atresia necessitating surgery.

The more serious causes are due to middle ear infections, which may be chronic or acute. The classification of this type of infection is listed according to the classification of Tato, who called them postinfection sequelae of otitis media.

Chronic loss of hearing not due to infections is usually of the otosclerotic type, is hereditory, and may be encountered in adolescence, but rarely in childhood. The ways in which pediatricians may prevent deafness in their patients are discussed.

Since the articles on the antibiotics which occupy most of this number have fairly adequate summaries in English, I abstracted one which had no summary in English.

Some Clinical and Epidemiological Aspects of Intoxication Due to Drugs Commonly Used in Infancy.—The authors studied in detail 153 cases from a total of 266 cases brought into the emergency service of the children's hospital in 1956. The cases studied were due to drugs commonly used in pediatric practice or to drugs used by another member of the family. The largest group received drugs given by members of the family; in the second group the drugs were taken by accident; in 13 cases misunderstanding of the doctor's orders was responsible.

The drugs responsible were codeine, barbituates, sedatives like chlorpromazine, rawolfia, atropine salts, and antiparasitic drugs. In young children cough mixtures with codeine were found not infrequently. Salicylates and sulfonamides were not as common as might be expected.

The authors outline diagnostic problems and predominant symptoms, which were hyperthermia, diarrhea, bronchopneumonia, acidosis, vomiting, unconsciousness, and petechial hemorrhages.

In the tranquilizer groups, there were hypotonia, hypothermia, nystagmus, stupor, excessive mucus formation in the posterior pharynx, and tachycardia.

There is a special need for further education of both physicians and the public in this problem. The manufacturers of drugs and pharmacists must also be on the alert.

Canadian Medical Association Journal, Montreal

Abstracted by H. M. Keith, M.D.

78, No. 9 (May 1) 1958

* Abdominal Pain of Cerebral Origin in Children. John Stobo Prichard.—p. 665.
Infantile Scurvy in Manitoba. David Grewar.—p. 675.

Abdominal Pain of Cerebral Origin in Children.—Nineteen children with abdominal pain, believed to be of cerebral origin, were studied. Their ages ranged from 2 to 13 years. In each case the presenting complaint was abdominal pain, without localized cause and not the aura of a convulsion. They could be divided into two groups, the first, and commoner, being characterized by attacks lasting an hour or more, often associated with nausea, vomiting, or headache. There was frequently a family history of migraine. It is suggested that these cases were examples of abdominal migraine.

The second group was characterized by attacks lasting 5 or 10 minutes and associated in some instances with confusion, vasomotor disturbances, nausea, or vomiting. A family history of migraine was not characteristic, and the electroencephalogram showed evidence of discharges in the temporal region. It was felt that these were examples of true abdominal epilepsy.

Journal of Clinical Endocrinology and Metabolism, Springfield, Ill.

Abstracted by Judson J. Van Wyk, M.D.

18, No. 1 (Jan.) 1958

* Eunuchoidism with Low Urinary Follicle-Stimulating Hormone in the Female. M. P. Moldawer, F. Albright, P. H. Benedict, A. P. Forbes, and P. H. Henneman.—p. 1.
Urinary Estrogen Excretion in Cushing's Syndrome. C. D. West, B. Damast, and O. H. Pearson.—p. 15.
Metabolism of Epinephrine Containing Isotopic Carbon in Man. O. Resnick and F. Elmadjian.—p. 28.
Metabolism of Free and Conjugated 17-OHCS in Uremia. E. Englert Jr., H. Brown, D. G. Willardson, S. Wallach, and E. L. Simons.—p. 36.
Plasma 17-OHCS Levels in Patients with Abnormal Glucose Tolerance During Pregnancy. B. Little, V. K. Vance, and E. Rossi.—p. 49.
Thyroid Function in Subacute Thyroiditis. R. Volpe, M. W. Johnston, and N. Huber.—p. 65.
Some Aspects of Thyroidal Iodine Metabolism in Iodine-Induced Hypothyroidism. K. R. Paley, E. S. Sobel, and R. S. Yalow.—p. 79.
The Plasma Proteins in Thyroid Disorders. R. Greene, D. C. Morgan, and R. Bird.—p. 99.

Eunuchoidism with Low Urinary Follicle-Stimulating Hormone in the Female.—Four cases are presented of a syndrome in the female characterized by sexual infantilism, eunuchoidal skeletal proportions, female sex chromatin pattern, and absence of urinary gonadotrophins on repeated assay. The youngest of these patients was 28 years of age, making it unlikely that these patients simply had a physiologic delay in the onset of adolescence. No debilitating disease or associated endocrine abnormality could be demonstrated in any of the patients. The syndrome is contrasted with the comparable syndrome in the male and with the syndrome of eunuchoidism with high FSH in the female. Although the syndrome is thought to be of pituitary origin, no response could be demonstrated to injections of human chorionic gonadotrophin or pregnant mare serum.

Medizinische Klinik, Munich

Abstracted by Samuel Amberg, M.D.

53, No. 14 (April) 1958

* Rotation Osteotomy as Prophylactic Procedure for the Improvement of the Results of Treatment of Congenital Dislocation of Hips. M. Lange.—p. 566.
Formation and Deformation of the Head. C. Krauspe.—p. 568.
* Stenosis of the Isthmus of the Aorta: Symptomatology, Surgical Treatment and Evaluation of Results. B. Schlegel and E. Stein.—p. 531.

53, No. 15 (April) 1958

* The Mesenchymal Reaction on Loss of the Spleen of Healthy Individuals. A Stömer and E. Kautzsch.—p. 628.

53, No. 16 (April) 1958

* Drug Treatment of Spastic Paraplegia. H. Thom.—p. 714.

53, No. 17 (April) 1958

* The Changes of Serum Protein in Infancy. G. W. Schmidt.—p. 747.

53, No. 19 (May) 1958

* Meprobamate for Adaptation Difficulties of Children. H. Linzenich.—p. 840.

Rotation Osteotomy as Prophylactic Procedure for the Improvement of the Results of Treatment of Congenital Dislocation of Hips.—A detailed description is given of an osteotomy to correct anterotation and to insure the fixation of the neck of the femur. The advantages of the procedure are discussed.

Stenosis of the Isthmus of the Aorta: Symptomatology, Surgical Treatment and Evaluation of Results.—The symptomatology of stenosis of the isthmus of the aorta (coarctation) is discussed on the basis of 22 observations. Of these, 20 were subjected to surgery, 2 cases at the age of 7 years, 1 at 10 years, 4 at an age before 15 years, and 4 before 20 years of age. Of the objective signs, arterial pressure of upper and lower extremities, oscillography and dynamic of pulse, and x-ray examination are discussed in some detail. Auscultation and sound recordings before and after surgery and electrocardiography are also discussed. Indications for surgery and surgical methods receive attention. It is stated that the most favorable age for operation is from the 5th to the 20th year of life. Mortality and its causes and the results of surgery are outlined, with use particularly of the collective statistics of the American College of Chest Physicians (1957). Any noteworthy elevation of blood pressure in childhood should suggest the possibility of isthmus stenosis.

The Mesenchymal Reaction on Loss of the Spleen of Healthy Individuals.—Previously healthy spleens were removed from 12 adults after accidents. Various morphological changes in blood and bone marrow are tabulated from data in the literature. The frequency of certain changes is noted, for instance, the appearance of marrow cells and diminution of antibody formation occurs always. A decrease of serum albumin and increase in serum globulin occurs in most cases, while bleeding and coagulation times are not influenced. Altogether 34 items are registered. The main object is the medical evaluation for compensation, and it is concluded that removal of the spleen decreases the functional capacity of the patient by 20%.

Drug Treatment of Spastic Paraplegia.—Patients with spastic paraplegia due to transverse cord lesions were treated with Akineton (3-piperidine-1-phenyl-1-bicyclo-heptenyl-propanol), which has a ganglioplectic and myospasmolytic activity. Patients with cerebral infantile paralysis also received this medication. The drug gave better results than other drugs, although its effect is limited. The hyperhydrosis was often markedly inhibited.

The Changes of Serum Protein in Infancy.—The author refers to his own previous publications and reports in the literature, and the changes in the total protein content of the blood serum and the various protein fractions during the first year of life and the influence of various diseases thereupon are reviewed.

Meprobamate for Adaptation Difficulties of Children.—The administration of meprobamate facilitated the adaptation of children to the hospital. A more extensive publication is anticipated.

Monatsschrift für Kinderheilkunde, Berlin

Abstracted by Hans Hartenstein, M.D.

105, No. 10 (Oct.) 1957

Arteriosclerosis, Especially of the Coronary Vessels, in Childhood. W. Janssen.—p. 361.
* The Cerebral Phase of Cytomegalic Inclusion Body Disease. J. Oehme.—p. 366.
Biological Data Regarding Development of the Paranasal Sinuses in Childhood. F. Schmid and E. W. Voelckel.—p. 367.

Treatment of Fresh Burns of the Upper Digestive Tract Due to Caustic Agents and Heat and Their Late Effects in Childhood. Klaus Schoenfeld.—p. 369.

* Serial Nephelometric Erythrocyte Resistance Determinations in Premature Infants. H. Gerbstaedt, U. Gerbstaedt, and H. Herold.—p. 373.

Stenosis of the Ureteral Ostium and Ureterocele: Diagnosis and Treatment in Childhood. E. Willich.—p. 377.
Bipolar and Unipolar Electrocardiography in Premature Infants. Joachim Stoermer.—p. 386.
Case Reports: Congenital Intestinal Atresia with Pancreatic Anomaly. Bernd Gumbel.—p. 389.
Death Due to Crush-Syndrome Following Prolonged Whipping. F. Schleyer and W. Pioch.—p. 392.

The Cerebral Phase of Cytomegalic Inclusion Body Disease.—Cytomegalic inclusion body disease is an illness caused by a virus possessing facultative pathogenicity. The cerebral form in the young infant is characterized by spasms and encephalitic manifestations. Cerebral malformations, microcephaly, or hydrocephalos can frequently be demonstrated. Periventricular and intracerebral calcifications occurring concurrently may make differentiation from toxoplasmosis difficult. Brain damage due to this disease acquired during infancy may later lead to mental deficiency.

Serial Nephelometric Erythrocyte Resistance Determinations in Premature Infants.—Erythrocytes of premature infants did not show decreased resistance to hypotonic saline solution. However, this finding could not be correlated with the intensity of duration of icterus neonatorum.

Two osmotically different erythrocyte populations were demonstrated in 6 of 21 premature infants during their periods of anemia of prematurity. This finding could not be explained clinically, and it was speculated that there was a connection between it and the reticulocytosis occurring during this period.

News and Comment

GENERAL NEWS

Children's Bureau Clearinghouse for Research.—The Children's Bureau Clearinghouse for Research in Child Life is now entering its tenth year of service. On the basis of its experience in publishing *Research Relating to Children,* several changes in its policy have been made.

The Clearinghouse is widening the scope of *Research Relating to Children* to cover the important area of programs and services, in addition to child-centered research. Consequently, the Clearinghouse is now soliciting reports of research on programs and services for children in the health and welfare fields.

Since apparently few of the "consumers" of *Research Relating to Children* found the sections on "Pregnancy and the Newborn" and "Physical Health and Disease" of great interest, research in these two categories will no longer be included. Only those studies of physical health will be included which are of interest to investigators in fields other than the strictly medical sciences, such as studies of physical growth, psychosomatic illness, and emotional or social factors in health and disease. The Clearinghouse is no longer soliciting reports of studies concerned principally with the physical aspects of disease or therapy.

Investigators using *Research Relating to Children* regularly have felt that the masters' theses included in the publication did not justify the space. Therefore, except where the work represents work beyond a doctorate, as in dentistry, theses at the masters' level will no longer be included.

The only free copies available are those sent to the investigator who reports a study in a specific issue. Others may purchase copies of *Research Relating to Children* through the Government Printing Office at whatever price covers the cost of printing the individual issue. The present issue is $1.00.

Persons on the regular mailing list will be notified when an issue is released; those who are not now on the list but who wish to be should write to the Clearinghouse. In recent years the demand has exceeded the number of copies the Clearinghouse could supply within its budget. For this reason, *Research Relating to Children* is now available through the Government Printing Office. Investigators reporting to the Clearinghouse have indicated that, by and large, they do not oppose the unrestricted distribution associated with the sale of the publication.

In an effort to keep current, *Research Relating to Children* will be published twice a year. Brief reports of long-term research programs will be included in each issue. Insofar as possible, the Clearinghouse will attempt to provide publication information on studies reported in earlier issues.

Inquiries and reports of research should be directed to the Clearinghouse for Research in Child Life, Children's Bureau, Social Security Administration, U. S. Department of Health, Education, and Welfare, Washington 25, D. C.

ANNOUNCEMENTS

University of Colorado Fellowships.—The Department of Pediatrics of the University of Colorado Medical Center announces fellowships in pediatrics in allergy, infectious disease, hematology, and premature and newborn nursery. Applicants should be graduates of approved schools of medicine and should have completed at least one or more years of hospital training. Preference will be given to those who are in the course of completing the pediatric hospital training required for the examination of the American Board of Pediatrics. The fellowships, for one or two years, include fundamental laboratory research and clinical investigation, as well as training in clinical diagnosis and management.

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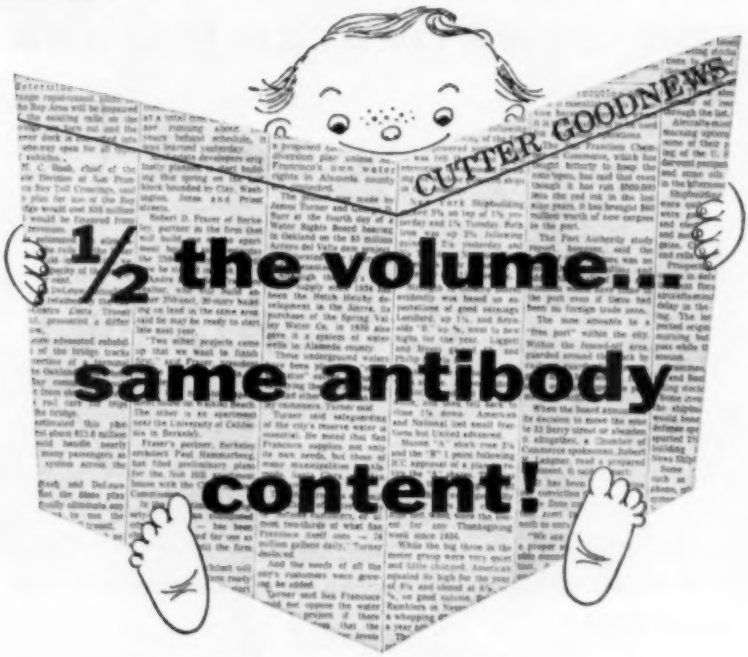

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1. Goodman, L., and Gilman, A.: Pharmacological Basis of Therapeutics, New York, Macmillan, 1955, p. 1153. 2. Brown, H. W., *et al.*: J.A.M.A. *161*:515 (June) 1956. 3. Hoekenga, M. T.: World M. J. *3*:299 (Sept.) 1956.

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